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CONTENTS OF VOLUME 38

JULY, 1926. NUMBER 1

PAGE

Insensible Perspiration: Its Relation to Human Physiology and Pathology. Francis G. Benedict, Ph.D., and Howard F. Root, M.D., Boston..... 1

The Rate of Urea Excretion as a Test of Renal Function by Means of a Modification of McLean's Index. Shohei Kawahara, M.D., Rochester, Minn. 36

Gastric and Duodenal Ulcer: Frequency, Number, Size, Shape, Location, Color, Sex and Age in Seven Thousand Seven Hundred Necropsy Records at Bellevue Hospital, New York. Mills Sturtevant, M.D., and Louis L. Shapiro, M.D., New York..... 41

Edema: I. Correlation of Elastometer Findings, Disappearance Time for Intradermally Injected Salt Solution, Urinalysis and Nitrogen Retention of the Blood in Edema. Margarete Meta Kunde, Ph.D., Chicago 57

Stenosis of the Isthmus (Coarctation) of the Aorta and Its Diagnosis During Life: Report of Four Cases. John T. King, Jr., M.D., Baltimore 69

The Rôle of Insulin in Protein Metabolism. N. W. Janney, M.D., and I. Shapiro, M.D., Los Angeles..... 96

The Relative Importance of the Systolic and the Diastolic Blood Pressure in Maintaining the Coronary Circulation. Fred M. Smith, M.D.; G. H. Miller, M.D., and V. C. Graber, M.D., Iowa City..... 109

Auricular Fibrillation with Regular Ventricular Rhythm and Rate Over Sixty. Robert L. Levy, M.D., New York..... 116

External Factors Causing Variable Results in the Kottmann Reaction. Jacob Kasanin, M.D., and Emily Knapp, A.B., Boston..... 129

Water Metabolism: IV. Sugar Metabolism in Dehydration. Edmund Andrews, M.D., Chicago..... 136

Book Reviews 142

AUGUST, 1926. NUMBER 2

Clinical Physiology of the Stomach: Simultaneous Quantitative Observations on Gastric Secretory Volume, Acidity and Motility. Arthur L. Bloomfield, M.D., and Chester S. Keefer, M.D., Baltimore..... 145

Hypertension and Constipation: A Statistical Inquiry. Walter C. Alvarez, M.D.; R. L. McCalla, M.D., and A. Zimmermann, Dr.ès.Sc., San Francisco 158

Diseases of the Liver: V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System. Carl H. Greene, M.D., and H. Milton Conner, M.D., Rochester, Minn..... 167

Persistent Premature Contractions: A Clinical Study. Harold L. Otto, M.D., and Harry Gold, M.D., New York..... 186

PAGE

The Rationale of Therapeutic Puncture in Pericardial Effusions: An Experimental Study. Charles Spencer Williamson, M.D., and Harold N. Ets, M.S., Chicago 206

The Relation of Monilia to Infections of the Upper Air Passages. A. J. Kotkis, M.D.; M. Wachowiak, M.D., and Moyer S. Fleisher, M.D., St. Louis 217

Coronary Thrombosis with Congenital Absence of the Left Coronary Artery. Fred M. Smith, M.D., and V. C. Graber, M.D., Iowa City 222

Mycotic Aneurysms: A Report of Two Cases. Roscoe D. Leas, M.D., and Harvey S. Thatcher, M.D., Cleveland 226

Gastric Ulcer: IV. Experimental Production of Gastric Ulcer by Local Anaphylaxis. Phillip F. Shapiro, M.S., and A. C. Ivy, Ph.D., M.D., Chicago 237

The Unitary Nature of Impairment of Renal Function. Arthur M. Fishberg, M.D., New York 259

Book Reviews 276

SEPTEMBER, 1926. NUMBER 3

The Occurrence of Benign Glycosuria in Diabetic Families. J. E. Holst, M.D., Copenhagen, Denmark 279

Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and Their Relationship. Roy R. Grinker, M.D., Chicago 292

The Effect of Atropine on Gastric Function in Man: A Quantitative Study. Chester S. Keefer, M.D., and Arthur L. Bloomfield, M.D., Baltimore 303

The Treatment of Polycythemia Vera (Erythremia) with Phenylhydrazine. George E. Brown, M.D., and Herbert Z. Giffin, M.D., Rochester, Minn. 321

The Pathogenesis of Lipoid Nephrosis. Herman Elwyn, M.D., New York.. 346

Epigastric Pulsation: The Diagnosis of the Arrhythmia Cordis Through the Epigastriogram. Nobutatsu Fukui, M.D., Tokyo 360

Mycotic Aneurysm of the Aorta. Fred M. Smith, M.D., and G. H. Hansmann, M.D., Iowa City 367

The Pharmacology and Therapeutics of Novasurol. A. M. Serby, M.D., Chicago 374

The Basal Metabolic Rate in Cases of Chronic Cardiac Disease and in Cases of Hypertension. Shepard Shapiro, M.D., New York 385

The Use of Sodoku in the Treatment of General Paralysis: A Preliminary Report. H. C. Solomon, M.D.; A. Berk, M.D.; M. Theiler, M.R.C.S., and C. L. Clay, M.D., Boston 391

Acute Cocaine Poisoning and Its Treatment in the Monkey (Macacus Rhesus). A. L. Tatum, M.D., and K. H. Collins, B.S., Chicago 405

Book Reviews 410

OCTOBER, 1926. NUMBER 4

Glandular Fever (Infectious Mononucleosis). C. W. Baldridge, M.D.; F. J. Rohner, M.D., and G. H. Hansmann, M.D., Iowa City 413

Lipoid Nephrosis. Francis D. Murphy, M.D., and Louis M. Warfield, M.D., Milwaukee 449

PAGE

Carcinoma of Cortex of Suprarenal Gland with Virilism: Report of a Case with Necropsy. Henry M. Feinblatt, M.D., Brooklyn 469

Urea Retention: A Simple Method for Its Estimation by the Mercury Combining Power of Blood. Philip S. Hench, M.D., and Martha Aldrich, B.A., Rochester, Minn 474

The Formation of Organic Acids and the Retention of Chlorides in Lobar Pneumonia. Cai Holten, M.D., Copenhagen, Denmark 489

Changes in the Chemical and Physical Characteristics of the Blood Following the Administration of Parathyroid Hormone, with Special Reference to the Clotting of the Blood. A. Cantarow, M.D.; W. R. Caven, M.B. (Tor.), and Burgess Gordon, M.D., Philadelphia 502

The Quantities of Serum Albumin, Globulin and Fibrinogen in the Blood Plasma in Acute and Chronic Nephropathies. George Fahr, M.D., and W. W. Swanson, M.D., Minneapolis 510

The Combining Power of Proteins with Rose Bengal: II. Application as a Quantitative Test on the Spinal Fluid. Sanford M. Rosenthal, M.D., and F. Douglas Ackman, M.D., Montreal, Canada 527

Peristalsis in a Loop of Small Intestine: A Direct Study. Laurence E. Hines, M.D., and H. C. A. Mead, M.D., Chicago 536

Aid in the Diagnosis of Typhoid Fever: A New Laboratory Method. C. A. Mills, M.D., and K. V. Kitzmiller, M.D., Cincinnati 544

Book Reviews 551

NOVEMBER, 1926. NUMBER 5

PAGE

Chemical Changes in the Blood During Fasting in the Human Subject. William G. Lennox, with the Assistance of Marie O'Connor and Margaret Bellinger, Boston 553

The Output of the Heart per Beat in Hyperthyroidism. I. M. Rabinowitch and Eleanor V. Bazin, Montreal 566

Roentgen-Ray Therapy in Erysipelas. E. S. Platou, M.D., and Leo Rigler, M.D., Minneapolis 573

A Modification of the Urea Concentration Test. Harold W. Jones, M.D., and Abram Cantarow, M.D., Philadelphia 581

The Basal Metabolism of the Japanese. Seizaburo Okada, M.D.; Eiichi Sakurai, M.D., and Toshio Kameda, M.D., Tokyo, Japan 590

The Mechanism of Pain in Gastric and Duodenal Ulcers: I. Achlorhydria. Walter Lincoln Palmer, M.D., Chicago 603

Renal Dwarfism: Report of a Case. Frederic W. Lathrop, M.D., Baltimore 612

Arachnidism: Spider Poisoning. Emil Bogen, M.D., Los Angeles 623

Nontraumatic Left Diaphragmatic Hernia: Clinical and Roentgenologic Studies in Fifteen Cases. Henry K. Pancoast, M.D., and Russell S. Boles, M.D., Philadelphia 633

The Regulation of the Flow of Bile and Pancreatic Juice Into the Duodenum. Glover H. Copher, M.D., and Shuichi Kodama, M.D., St. Louis 647

Direct Examination of the Gastric Juice: A New Functional Test. Arnold Galambos, M.D., New York 654

Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister. William F. Petersen, M.D., and David A. Willis, M.D., Chicago 663

Book Reviews 682

DECEMBER, 1926. NUMBER 6

PAGE

Analysis of Heart Sounds. H. B. Williams, M.D., and H. F. Dodge, S.B., A.M., New York 685

The Mechanism of Pain in Gastric and in Duodenal Ulcer: II. The Production of Pain by Means of Chemical Irritants. Walter Lincoln Palmer, M.D., Chicago 694

Chronic Biliary Tract Disease: The Diagnostic Criteria. John G. Mateer, M. D., and W. Stuart Henderson, M.B., Detroit 708

The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels. William F. Petersen, M.D., and George Milles, S.B., Chicago 730

Hyperthyroidism, Myxedema and Diabetes. Russell M. Wilder, M.D., Rochester, Minn. 736

Cardiac Capacity Determined by Standardized Effort: Preliminary Report. Joseph B. Wolffe, M.D., Philadelphia 761

The Basal Metabolism in Beriberi. Seizaburo Okada and Eiichi Sakurai, Tokyo, Japan 770

The Use of Insulin by Mouth. H. R. Miller, M.D., New York 779

The Growth of the Long Bones in Childhood, with Special Reference to Certain Bony Striations of the Metaphysis and to the Rôle of the Vitamins. H. A. Harris, M.B., St. Louis 785

Primary Carcinoma of the Thymus: Report of a Case. I. I. Lemann, M.D., and John Smith, M.D., New Orleans 807

The Spectrophotometric Analysis of the Color of the Skin, and the Observations by This Method in Normal and in Pathologic Subjects. Charles Sheard, Ph.D., and George E. Brown, M.D., Rochester, Minn. 816

Book Reviews 832

JUL 26 1926

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VOLUME 38 NUMBER 1

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CONTENTS OF PREVIOUS NUMBER

JUNE, 1926. NUMBER 6

Arteriosclerosis and Increased Blood Pressure: Experimental Production. Franklin R. Nuzum, M.D.; Beatrice Seegal, M.D.; Ruth Garland, M.D., and Margaret Osborne, M.S., Santa Barbara, Calif.

Diagnosis of Pulmonary Neoplasm. Maurice Fishberg, M.D., New York.

Water Metabolism: III. Dehydration Fevers. Edmund Andrews, M.D., Chicago.

Corrigan's Description of Aortic Insufficiency. Edited, with a Note, by Logan Clendening, Kansas City, Mo.

A Confirmatory Sign of Free Fluid in the Pleural Space: Preliminary Report. Martin Lasersohn, M.D., Richmond, Va.

Biliary System Function Tests. William P. Murphy, M.D., Boston.

The Diagnostic Aid in Evaluating the Vigor of Inspiratory Costal Excursion. C. F. Hoover, M.D., Cleveland.

A Method for the Continuous Quantitative Estimation of Gastric Secretion and Discharge in Man. Arthur L. Bloomfield, M.D., and Chester S. Keefer, M.D., Baltimore.

The Relation of the Erythrocyte Sedimentation Reaction to the Ability of Flocculation of the Plasma and Serum. E. H. Rubin, M.D., New York.

The Seasonal Variation in the Onset of Acute Diabetes: The Age and Sex Factors in 1,000 Diabetic Patients. S. Franklin Adams, M.D., Rochester, Minn.

Book Reviews.

Index.

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Archives of Internal Medicine

VOLUME 38 JULY, 1926 NUMBER 1

INSENSIBLE PERSPIRATION: ITS RELATION TO HUMAN PHYSIOLOGY AND PATHOLOGY*

FRANCIS G. BENEDICT, PH.D.
AND
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BOSTON

The changes that occur in the body weight from day to day or, indeed, from hour to hour are unnoticed by most persons, probably because the body weight is fairly constant for weeks at a time. Large losses in weight, such as those which result from extreme exercise and profuse perspiration, as in athletic contests, are easily recognized, but smaller losses or increases are not so apparent. Thus, during the day variations in body weight amounting to several pounds, directly attributable to the ingestion of food and drink and the passage of feces and urine, may not be noted because it is not the custom to record the body weight frequently throughout the day and often the appliance on which the body is weighed is not accurate enough to show changes in weight of less than 1 pound or 0.5 Kg. Such alterations in body weight are easily understood, however, because they are visible changes. But the weight of the food and drink is not entirely compensated by the weight of visible excreta. There is also an invisible loss of gaseous substance in the form of carbon dioxide and water vapor, given off both from the lungs and the skin. This invisible loss may sometimes amount to 70 Gm. in an hour, even though the subject is quiet and resting. The share that these invisible, gaseous losses play in the twenty-four hour loss in weight is today but imperfectly appreciated, although it was considered of great physiologic importance three or more centuries ago.

Sweat can be seen and this visible perspiration can readily be perceived to represent a loss of material from the body. The invisible loss is not so readily recognized and a delicate balance must be relied on to establish it. The appearance on a cold, frosty morning of condensed

* From the Nutrition Laboratory of the Carnegie Institution of Washington and the New England Deaconess Hospital, Boston.

* This paper is no. 63 of a series of studies in metabolism from the Harvard Medical School and allied hospitals, the expenses of which have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

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vapor in expired breath instantly shows, however, that such a gaseous loss is taking place. In addition, therefore, to the occasional and easily recognized changes in weight, such as the heavy losses experienced after severe muscular work (losses that may amount to 5 or 6 Kg. in an hour [1]) and the decided changes in weight caused by disease or by dieting, attention must be directed to the continuous invisible or insensible losses that take place from the lungs and skin. If the body weight of a normal person not performing sufficient muscular work to produce visible perspiration is determined from hour to hour on good scales, it will be found to decrease steadily until food is eaten, when it will rise in accordance with the weight of food or drink taken. It will subsequently decrease at a fairly regular rate until urine or feces is passed, at which time the loss will be exactly that represented by the weight of the excreta. With increased activity, even if not carried to the point of producing visible perspiration, there is a greater loss in weight. With the reduced activity of rest in bed, the loss decreases but nevertheless persists. These changes in weight were strikingly shown in a series of weighings of a subject in the chemical laboratory at Wesleyan University.[2]

The uncertainty with regard to the exact nature of the loss in body weight is nowhere better brought out than in the innumerable expressions coined by different writers to express this loss. Thus, the earliest expression was "perspiratio insensibilis." Subsequently various terms were employed, such as "insensible loss," "intangible loss," "water vaporization from the lungs and the skin," and more recently the expression "hourly loss." On classical grounds and pending a more careful analysis of the nature and character of this loss (which the Nutrition Laboratory is now investigating, particularly with regard to the proportions of water lost from the lungs and the skin), the terms "perspiratio insensibilis," "insensible perspiration" and "insensible loss" will be used in this article as the most convenient terms available at the present time.

By "perspiratio insensibilis" is commonly meant those gaseous emanations from the body which do not appear in the form of sensible moisture or sweat, in other words, the insensible, invisible, intangible but weighable gaseous and vapor productions arising from the lungs in the process of exhalation and from the skin by due process of vaporization, i. e., excretion of moisture and carbon dioxide. The original idea of this classification was undoubtedly to distinguish the invisible from the visible loss of material from the body occurring when there is considerable perspiration.

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1. Benedict, F. G., and Joslin, E. P.: A Study of Metabolism in Severe Diabetes, Carnegie Inst., Wash., pub. no. 176, 1912, p. 96, table 114.
2. Benedict and Joslin (footnote 1, p. 91, table 111).

From the definition of the "perspiratio insensibilis" it is obvious that the experimental attack must be along certain definite lines. Since the interest lies in the total loss in weight of the body under conditions in which visible perspiration does not occur, the simplest method is, obviously, to weigh the body from time to time and note this loss. The simplicity of this operation, however, is far offset by the difficulties encountered. A balance of sufficient rigidity to support a man weighing 90 or even 100 Kg., and of sufficient accuracy to indicate a loss in weight which may average not far from 30 Gm. per hour during a short period, is difficult to secure. Exactly this procedure has at times been followed in the past, however, and even in some of the most recent reports there are evidences of the successful use of a balance for determining this loss.

Quantitative physiologic measurements began, in a certain sense, with the determinations of the weight of the insensible loss, and the historical development of this problem reflects the development of the study of physiology. Indeed, unmistakable evidence of an understanding of the insensible loss of the body is shown in the classics of Hippocrates and Galen, a critical examination of whose writings has been made by Weyrich.[3] Since the research to be reported in this article represents a quantitative study of the insensible, gradual and continuous, though variable, losses in the body weight of human beings, exclusive of urine, feces, sputum and gross or visible perspiration, the researches of those earlier investigators who also made quantitative measurements of the "perspiratio insensibilis" should be at least briefly considered.

EARLIER QUANTITATIVE MEASUREMENTS OF THE "PERSPIRATIO INSENSIBILIS"

The first quantitative measurements of the insensible loss were made by Sanctorius[4] in 1614, by means of an extremely ingenious steelyard. Suspended on a movable platform attached to this steelyard, he made innumerable measurements of his own loss in weight. Indeed, his records suggest that he carried these weighings out over a period of thirty years. Many of his curious aphorisms derived from findings with this balance have been quoted in the literature frequently, but obviously his conclusions are at present chiefly of historic interest, because he emphasizes the "perspiratio insensibilis." Some of his comments agree

3. Weyrich: Die unmerkliche Wasserverdunstung der menschlichen Haut, Leipzig, 1862.

4. Sanctorius: Medicina Statica, translated by John Quincy, Ed. 2, London, 1720. Lusk, in his History of Metabolism, in Barker's Endocrinology, New York, 1922, **3**:7, has reproduced a picture of Sanctorius suspended on his balance and has incorporated several of his aphorisms. Reference should also be made to King, J. T.: Basal Metabolism, Baltimore, 1924, frontispiece.

and others disagree with present findings. Sanctorius published no protocols and gives no idea of the sensitivity of his balance.

The results of Sanctorius immediately stimulated a number of other investigators. Among them was Dionysius Dodart [5] (1634-1707) in Paris, whose observations likewise extended over thirty years and who pointed out a striking difference in the perspiration during the summer and winter. Keill [6] in 1730 made observations during a complete year and then at intervals over nearly a decade. The work of Sanctorius and many of his followers is given in excellent abstract by Weyrich.[5] Reference should be made to Robinson,[7] Rye [8] and De Gorter [9] of Europe and particularly to Dr. John Lining of Charleston, S. C., for as Weyrich points out, Lining's report was the most complete of any published up to that time.

In 1740 Lining [10] made an extensive series of observations on himself, which extended throughout the greater part of a year. He weighed himself each morning immediately after rising and again at night, just before going to bed. The balance used is not described, but according to the data reported it weighed in pounds, ounces and drachms. The actual loss in weight is recorded in ounces and decimals of an ounce. Although Lining's measurements were made nearly 200 years ago, his plan of study was comprehensive and merits attention today,[11] but because of the inherent inaccuracies in his method, his findings cannot be considered of great value. His discussion deals chiefly with the influence of changes in season and the possible correlation between seasonal changes and the appearance of epidemic diseases in the South, which returned with great regularity at stated seasons. Lining attributes

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5. Dodart, Dionysius, cited by Weyrich: Die unmerkliche Wasserverdunstung der menschlichen Haut, Leipzig, 1862, p. 11.

6. Keill: Tentamina Medico-Physica quibus accedit Medicina statica britannica, Lugd. Batav., 1730. (Cited by Weyrich.)

7. Robinson: Treatise of the Animal Economy, Dublin, 1732; also Ed. 3, London, 1738; ibid. Dissertation on the Food and Discharges of Human Bodies, London, 1748. (Cited by Weyrich.)

8. Rye: Roger's Essay on Epidemic Diseases, Dublin, 1734 (Haller's Bibl. anatom., II, 272). (Cited by Weyrich.)

9. De Gorter: De perspiratione insensibili, Lugd. Bat., Ed. 2, 1736. (Cited by Weyrich.)

10. Lining: Philosophical Tr. **42**:491, 1742-1743; **43**:318, 1744-1745.

11. One can hardly find a finer expression of the true research drive in an isolated individual, over three thousand miles from any great physiologic centers, than is given by Lining in the introductory paragraph of his first paper, in which he states: "That candid and generous Principle which so universally possesses the Breasts of all true Friends to physical Literature, disposing them to give Assistance and Advice, even to such of the Illiterati who shew a Disposition of Inquiry after Truth; and that eminent Character you so justly bear in the Learned World; were sufficient Arguments with me, to lay before you, as a Specimen, one of my Meteoro-Statistical Tables: The Favour of your Opinion of the Method I have observed, will be most acceptable."

to the changes in season a pronounced influence on the insensible perspiration.

Although numerous other researches bearing on insensible perspiration were published after the work of Lining, particularly by Home, Hartmann and Martin, the brilliant period in the development of physiology and chemistry is represented by the work of Lavoisier. Lavoisier and Seguin [12] in 1790 emphasized for the first time the importance of separating the cutaneous respiration from the pulmonary respiration, and the significance of the latter as a path for the loss of water vapor and carbon dioxide. The interest at the moment, however, lies in their observations on the total insensible loss in weight of a man, which they reported as ranging from 11 to 32 grains per minute. Thus, according to their data the man lost from 0.583 to 1.7 Gm. per minute, or from about 900 to possibly 2,500 Gm. in twenty-four hours. This loss represents both the "cutaneous respiration and the pulmonary transpiration and respiration."

Although he gave no details of his balance and its sensitivity, Colin [13] in 1862 reported numerous measurements on himself made during repose and during activity. He found that his loss per hour, when he was quiet and asleep, varied from 28 to 30 and 35 Gm. per hour. When he was awake his loss was 50, 60 and 80 Gm., increasing even to 200 Gm. per hour with excessive exercise.

To study the insensible loss of fever patients, von Leyden [14] in 1869 used a balance which had a capacity of 3 centner, with a sensitivity of 1 loth (about 10 Gm.). His study is of interest as being the first in which a balance was used for pathologic cases.

In his classical study of the temperature of normal men, Jürgensen [15] in 1873 likewise recorded the body weight with a balance to within 10 Gm. Unfortunately, he gives no description of his balance and does not give the weights of food and drink, so that the insensible perspiration may not be computed.

After a lapse of twenty-five years, when apparently no measurements of the "perspiratio insensibilis" were recorded in the literature, Dennig [16] in 1898 reported the results of a careful study of the effect of reduction in the water intake. His series of values for the insensible perspiration

12. Seguin and Lavoisier: Mémoires de l'Académie des Sciences, Paris, 1790, p. 608; Oeuvres de Lavoisier, Paris, 1862, p. 711.

13. Colin: Bulletin Société Impériale et Centrale de Médecine Vétérinaire, 1862, 7, sér. 2, p. 208.

14. Von Leyden, E.: Untersuchungen über das Fieber, Deutsches Arch. f. klin. Med. **5**:308, 1869.

15. Jürgensen, T.: Die Körperwärme des gesunden Menschen, Leipzig, 1873, p. 27.

16. Dennig, A.: Die Bedeutung der Wasserzufuhr für den Stoffwechsel und die Ernährung des Menschen, Ztschr. f. diätet. u. physik. Therap. **1**:281, 1898.

of the one subject with whom he worked range from 320 Gm. per twenty-four hours on the sixth day of reduced water intake to 1,348 Gm. on the second day. Since, however, the body weights could be recorded only to the nearest 100 Gm., these figures are liable to considerable error. On the days when the water intake was increased, the insensible loss ranged from 230 Gm. on the first day to 1,065 Gm. on the fifth day. A second experiment on the same person showed a somewhat different picture. Dennig concludes that when a subject undergoes a second period of reduction in water intake, he has to a certain extent become accustomed to the conditions. The actual values for the insensible perspiration are not recorded for this second experiment.

In studying three obese individuals, Dennig [17] in 1899 again found considerable variability in the insensible perspiration from day to day. His protocols do not indicate that the daily activity was uniform, but variations as great as reported are difficult to explain on the basis of activity alone.

Using a balance reported as very sensitive, Bouchard [18] in 1899 recorded a gain in weight of human beings amounting to from 10 to 40 Gm. per hour, without any intake of liquid or solid material. This gain, he argues, is a convincing proof of the conversion of fat to carbohydrate. Bouchard's observations are of interest as an illustration of the use of the changes in total body weight rather than as proof of a transformation of fat to carbohydrate.

The use of an accurate balance to record the differences in weight from day to day was made about 1896 or 1897 by Atwater [19] and his associates in connection with the respiration calorimeter at Wesleyan University, Middletown, Conn. The subjects inside the respiration chamber were weighed at certain times each day on scales, sensitive to 10 Gm. Since in these experiments there was a complete measure of the income and outgo, the data are at hand for computing the insensible perspiration, for not only were the food and the drink accurately weighed, but likewise the amount of water vapor given off and later the oxygen consumption. In May, 1897, and subsequently experiments were made in which the data were secured for computing the insensible perspiration. In one experiment, which lasted three days, records were made of the daily change in weight, the entire change in weight at the end of the three days, the total weight of food and liquid consumed, and the total weight of urine passed. The feces, unfortunately, were

17. Dennig, A.: Die Bedeutung der Wasserzufuhr für den Stoffwechsel und die Ernährung des Menschen, Ztschr. f. diät. u. physik. Therap. **2**:292, 1899.

18. Bouchard, C.: Compt. rend. Soc. de biol. **127**:464, 1899.

19. Atwater, W. O., and Benedict, F. G.: Experiments on the Metabolism of Matter and Energy in the Human Body, U. S. Department of Agriculture, Office Experiment Station Bulletin 69, 1899.

not collected until the end of the fourth day, and it is necessary to assume that since 502 Gm. of feces were passed over a period of four days, 126 Gm. were passed on each of the three days of the experiment. This same criticism applies to three other experiments made during this series. In one three day experiment and three four day experiments it was found that subjects living inside a respiration chamber had an insensible loss per day of 1,105, 1,180, 1,211 and 1,344 Gm., respectively. The round value of 1,200 Gm. may be taken as the average for all four experiments. An insensible output of 50 Gm. per hour was therefore found in the case of men living in the narrow confines of a respiration chamber (at a temperature of not far from 20 C., with a relative humidity of the air of usually not far from 50 per cent), doing no work but not confined in bed. It was the custom in all of the respiration experiments at Middletown, Conn., to have the data so recorded as to permit the computation of the insensible perspiration, but it is not until the twenty-four hour period is given up and shorter experiments are made that the most accurate data with regard to the insensible perspiration are available.

The method of weighing the body as a means of determining the insensible perspiration reached its acme of perfection in the development and construction of an extraordinary balance by Lombard [20] in 1906. This balance, which graphically recorded the changes in weight, was extremely sensitive, being the combination of a true balance with a spring scale. One side was overweighted by 3 or 4 Gm., so that as the man lost weight the spring contracted, drawing the arm of the balance upward. A writing point connected with the balance arm was in contact with a kymograph drum, giving a record of the weight lost in approximately two minutes. Lombard gives curves showing the great sensitivity of his apparatus, and likewise some curves showing the actual changes in weight of a man while resting on the balance. Two men, weighing approximately 70 Kg. each, lost on the average about 40 Gm. per hour. In another series of experiments when the temperature was considerably higher, the total loss amounted to nearly 70 Gm. per hour, i. e., the loss was noticeably different with the same individual in a different environmental temperature. Professor Lombard [21] has given us permission to use certain data on three healthy medical students who were measured in 1906 and 1907. His average values are summarized in table 1.

As the result of 107 observations Professor Lombard finds that in an average room temperature of 19 C. the average loss in weight of

20. Lombard, W. P.: A Method of Recording Changes in Body Weight which Occur Within Short Intervals of Time, J. A. M. A. **47**:1790 (Dec. 1) 1906.
21. Lombard, W. P.: Recent personal communication to authors.

these medical students was 41.5 Gm. per hour. Professor Lombard also studied the loss from the air passages and from the skin alone. In the latter case he had each subject hold the breath for about twenty-seven seconds, during which time he noted the change in loss of weight on the balance. By this method he computes that the loss from the skin is about 24 per cent of the total loss. It is a matter of the greatest regret that this most promising, extraordinary piece of apparatus could not have been used further.

Zuntz, Loewy, Müller and Caspari [22] in 1906 used an excellent balance, sensitive to 10 Gm., which was evidently in the laboratory at the top of Monte Rosa. Differences in body weights were determined daily, and the insensible perspiration was calculated by making corrections for the sensible income and outgo. Since their gaseous metabolism also was known, the authors were able to compute the loss from the lungs, thus dividing the total insensible perspiration between the lungs and the skin.

TABLE 1.—*Insensible Loss in Body Weight of Healthy Medical Students (Lombard)*

Subject	Dates	Number of Observations	Body Weight, Kg.	Height, Cm.	Loss in Weight: Per Minute, Gm.	Loss in Weight: Per Hour, Gm.	Room Temperature, C.
1	Nov. 6-20, 1906	30	64.7	175	0.620	37.2	18
2	Jan. 18-30, 1907	27	67.0	175	0.729	43.7	19
3	March 19-28, 1907	28	61.5	173	0.785	47.1	21
4	Nov.-Dec., 1907	22	65.0	175	0.633	38.0	18
Average		107	64.5	175	0.692	41.5	19

Schwenkenbecher and Inagaki [23] in 1906, employing the method of weighing the body and all the intake and output of sensible material, in a series of experiments on two normal and eleven pathologic patients studied particularly the water exchange during fever. This research illustrates the practical use of the determination of the insensible perspiration in pathology. The body weight was apparently recorded only to within 100 Gm., but the experiments lasted approximately a week, so that the error was thus minimized. The two normal subjects showed water equilibrium in seven days. On the other hand, the fever patients showed a material water loss. The authors point out that this does not mean that there may not be an actual increase of water in the body,[24]

22. Zuntz, N.; Loewy, A.; Müller, F., and Caspari, W.: Höhenklima und Bergwanderungen, Ed. 1, Berlin, 1906, p. 377.

23. Schwenkenbecher, A., and Inagaki: Ueber den Wasserwechsel des fiebernden Menschen, Arch. f. exper. Path. u. Pharmakol. **54**:168 (Feb.) 1906.

24. Schwenkenbecher, A., and Inagaki: Ueber den Wassergehalt der Gewebe bei Infektionkrankheiten, Arch. f. exper. Path. u. Pharmakol. **55**:203, 1906.

for the fever patients lost more organic body material than did the normal persons.

In studying the influence of sodium chloride on metabolism, Tuteur,[25] in 1910, in Schwenkenbecher's clinic, obtained on himself an excellent series of twenty-four hour determinations of the insensible perspiration on sixty-one consecutive days, with reasonably uniform daily habits of life and diet. Most careful consideration was given to the weights of food, drink, urine and feces. The uniformity in his results from day to day is striking, especially since during the entire time he carried out his usual laboratory activities. Thus, the average loss per twenty-four hours during the first sixteen days was 1,474 Gm.; during the next twenty days 1,429 Gm.; during the next five days 1,655 Gm.; during the next sixteen days 1,523 Gm., and during the last four days 1,578 Gm.

The twenty-four hour insensible perspiration was determined in 1910 by Caspari [26] in Durig's Monte Rosa expedition, in periods both of quiet and during marching. With the exception of one series of rest experiments, considerable variations were noted in the loss from day to day under seemingly the same conditions of activity. These variations are probably accounted for by the fact that the balance used by the author was, as he emphasizes, very unsatisfactory.

In an investigation on the relation of the loss of water from the skin and lungs to the external temperature, Osborne,[27] working in Australia in 1910, measured the loss in body weight by means of a very sensitive balance, called by him a "human balance," with which he claimed that the weighings were taken to the nearest gram. The experiments differed from the usual tests in that the balance was kept in a cool room in a wooden house about 20 yards from a hammock, suspended under a tree. In this series of experiments the subject was weighed very carefully; he then walked to the hammock and lay down quietly for an hour, when he was again weighed. All the measurements were made in the morning, covering a period of one hour. Occasionally a second experiment of one hour was carried out in the afternoon. Because of the very large differences in temperature (both of the dry and the wet bulb), the movement of air and the variations in the clothing worn, large differences in the loss of weight are recorded by Osborne.

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25. Tuteur, R.: Ueber Kochsalzstoffwechsel und Kochsalzwirkung beim gesunden Menschen, Ztschr. f. Biol. **53**:361, 1910.

26. Caspari, W.: Ueber den Stoffwechselversuch in Alagna und über die Einwirkung kurzdauernden Aufenthaltes in grösseren Bergeshöhen auf den Stoffwechsel, Denkschr. d. math.-naturwissensch. Klasse d. kaiserl. Akad. d. Wissensch. **86**:483, 1910.

27. Osborne, W. A.: The Relation of Loss of Water from the Skin and Lungs to the External Temperature in Actual Climatic Conditions, J. Physiol. **41**:345 (Dec.) 1910.

Thus, in the rest experiments the hourly loss in weight varied from 362 Gm. to as low as 44 Gm. In one experiment in which he chopped wood, the loss in weight was 840 Gm. per hour. Walking in the shade produced in one instance an increase of about 100 per cent. in the weight loss. Osborne also simultaneously measured and analyzed the expired air with a Zuntz apparatus.

Numerous experiments with subjects both at rest and during work were made by Benedict and Carpenter [28] in the Middletown calorimeter in 1910. The scales had a sensitivity of 10 Gm. Practically all the experiments were made at a uniform temperature of about 20 C., and the humidity was in general low. In the rest experiments the loss varied considerably, depending on the nature of the experiment, the size of the subject, and whether food was given or not, ranging from as high as 79 Gm. per hour in a four hour experiment with one subject to as low as 23 Gm. with another subject, at the end of a fast of about a week's duration. The results of all the rest experiments, representing 158 days and over 2,000 hours of observation, showed that the insensible perspiration of normal, healthy men while sitting, lying asleep or awake, or engaged in minor activities, is on the average 40 Gm. per hour, with evidence of a pronounced influence of food and muscular activity. During severe muscular work the losses were much greater, about 200 Gm. per hour, and in one case 276 Gm. Since, however, in these cases there was a large amount of visible perspiration, the comparison with the rest experiments, in which only invisible perspiration played a rôle, must be made with considerable caution.

Although they present no new data with regard to the insensible perspiration of either normal or pathologic cases, Benedict and Joslin [29] in 1912 included in their report on metabolism in severe diabetes a consideration of the changes in body weight which may occur throughout the twenty-four hours, together with some discussion of the character and nature of these changes in weight, with special reference to the loss and gain of water by the body.

In connection with their expedition to the Alps, Galeotti and Signorelli [30] in 1912 determined their own insensible loss with an accurate balance (sensitivity 10 Gm.) at the laboratory on the top of Monte Rosa. Using an average value for oxygen consumption previously determined by Zuntz and Durig, they also computed the loss from

28. Benedict, F. G., and Carpenter, T. M.: The Metabolism and Energy Transformations of Healthy Man During Rest, Carnegie Inst., Washington, Pub. no. 126, 1910, p. 114.

29. Benedict, F. G., and Joslin, E. P.: A Study of Metabolism in Severe Diabetes, Carnegie Inst., Washington, Pub. no. 176, 1912, p. 89.

30. Galeotti, G., and Signorelli, E.: Ueber die Wasserbilan während der Ruhe und bei der Anstrengung im Hochgebirge, Biochem. Ztschr. **41**:268, 1912.

the lungs and that from the skin alone. They found considerable differences in the proportion of water lost from the lungs and skin, and from these findings drew conclusions with regard to the water balance.

Laying special stress on the loss in weight of the body and particularly during work, Boussaguet [31] in 1912 carefully determined the loss in weight, which he considered as due to loss of water. For these measurements he employed a balance which could weigh from 60 to 100 Kg. with an accuracy of 5 Gm. His results, which unfortunately were not accompanied by metabolism measurements, showed considerable irregularity at times in the loss per hour during seemingly equal work. The effect of air movement was very pronounced. The air was excessively moist.

Ideal conditions for determining the insensible perspiration existed in a study of a fasting subject by Benedict [32] in 1915. The loss in body weight was determined on scales sensitive to 10 Gm., and records were kept of the weights of urine, feces and drinking water, so that the insensible perspiration was readily computed. Furthermore, since the fasting subject underwent a regular daily routine for thirty-one days, his losses from day to day are reasonably comparable. At the beginning of the fast the insensible loss was about 45 to 50 Gm. per hour, falling off to an absolute minimum of 15 Gm. per hour on the twentieth day of fasting, and rising again toward the end of the fast to 22 and 26 Gm. per hour.

Emphasizing the importance in the clinic of a knowledge of the insensible perspiration, Isenschmid [33] in 1918 pointed out that the insensible perspiration is equal to the weight of the water given off, plus the weight of the carbon dioxide given off, minus the weight of oxygen consumed. From the diet one can compute the amount of carbon dioxide produced and the oxygen required to oxidize the food. Hence, if the subject is in metabolic equilibrium, one can compute in this way the insensible water loss.

In practice in the clinic Krehl [34] in 1919 made use of measurements of the insensible perspiration, particularly in studying disturbances in water balance and in the use of digitalis. His balance was not very sensitive, having an accuracy only of from 50 to 100 Gm., but he states that the method of determining the insensible loss from body weights and weights of urine and feces has been employed in his clinic for many

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31. Boussaguet: Recherches expérimentales sur les conditions physiologiques du travail des mineurs, Paris, 1912.

32. Benedict, F. G.: A Study of Prolonged Fasting, Carnegie Inst., Washington, pub. no. 203, p. 84, 1915.

33. Isenschmid: Die Bestimmung der Wasserbilanz am Krankenbett, Med. Klin. **14:**1128, 1918.

34. Krehl: Zur Kenntnis des Digitalisgebrauchs und des Wasserwechsels, Deutsches Arch. f. klin. Med. **128:**165, 1919.

years. This measurement was entirely aside from the daily weighing of the patient to control the water intake.

The pathologic significance of the insensible perspiration of children played a considerable rôle in Nobel's [35] discussion in 1919 of the importance of limiting the water output by diet. Nobel, in Pirquet's clinic, in Vienna, determined the insensible perspiration indirectly from the weight of the body and the weight of the intake and output, but gave no computations.

In studying the energy requirements of numerous groups of girls from 12 to 17 years of age, Benedict and Hendry [36] in 1921 determined on scales sensitive to 10 Gm. the weight of each girl just before going to bed and on rising in the morning. Six different groups, each including eleven or twelve girls, were studied during the night while sleeping in a respiration chamber at a temperature of about 20 C., with 40 per cent relative humidity. The average insensible perspiration per person during the night was found to be 38, 31, 32, 45, 34 and 32 Gm. per hour, respectively. On the basis of a kilogram of body weight the loss averaged from 0.63 to 0.93 Gm. per hour, with no evidence of any influence of slight differences in humidity.

Two other groups of girls, 18 and 14 years of age, respectively, were also studied by Benedict [37] in 1923. The measurements were made during an eight hour period at night in the respiration chamber, and the insensible perspiration for each group was found to be essentially the same, namely, 33 Gm. per hour. Individual losses ranged from as low as 18 Gm. to as high as 45 Gm. per hour.

In a consideration of pneumonia in infants, Meyer [38] in 1923 made use of the insensible perspiration determined by a balance which had a sensitivity of from 1 to 2 Gm. Since he found that the loss in weight was only from about 8 to 15 Gm. per hour, the error with this balance was large and he therefore had another balance constructed which was capable of weighing 15 Kg. to within 0.1 Gm. With this balance, although it took half a minute to secure equilibrium and the child might lose 0.1 Gm. during this time, Meyer states that he could weigh the loss during ten minutes with a precision of about 5 per cent. All the work was done with children, and usually in a fairly standard environment. In one typical case the loss was 7 Gm. per hour when the child was

35. Nobel, E.: Ueber den Wasserhaushalt des kindlichen Organismus, die Grenzen der Wasserentziehung und ihre systematische Anwendung bei pathologischen Zuständen, Ztschr. f. Kinderh. **22**:1, 1919.

36. Benedict, F. G., and Hendry, M. F.: The Energy Requirements of Girls from Twelve to Seventeen Years of Age, Boston M. & S. J. **184**:217, 257, 282, 297, 329 (March) 1921.

37. Benedict, F. G.: The Basal Metabolism of Young Girls, Boston M. & S. J. **188**:127 (Feb.) 1923.

38. Meyer, Jean: La broncho-pneumonie du nourrisson, Paris, 1923.

asleep, 10 Gm. when he was awake and quiet, and 14 Gm. when agitated and crying. He also found that generally there was an increased loss immediately after feeding, but subsequently a rapid decrease. He studied the factor of clothing, and also made some experiments with nude infants. These experiments were difficult to carry out. They were usually accompanied by a pronounced fall in rectal temperature, and occasionally the children were cold and moved about considerably. The removal of clothing apparently had little effect. Temperatures from 18 to 23 C. were without significance, but above 23 C. there was a somewhat larger loss. He concludes that humidity has little, if any, effect, although his evidence is based on only one experiment. Finally, he considers that the twenty-four hour loss, calculated from weighings on the balance over a period of two hours, has a significant relationship to the total intake of water in food and drink, a relationship that is of real clinical assistance. Thus, the normal relation of the twenty-four hour loss of water to the total intake of water is 42 per cent. In a case of eczema the relationship was 50 per cent; with an atrophic infant it was 54 per cent, while with three "hypotrophiques débiles" the ratio was from 24 to 34 per cent.

In 1925 Meyer [39] made practical use of the insensible perspiration in treating cases of eczema by the milk diet, as he considers that the withholding of water is an important factor in treating eczema.

Just after completing our manuscript, we received from Dr. Meyer further measurements [40] of the insensible perspiration of infants, evidently made with the same scales that he used in 1923. Meyer concludes that under conditions of repose and with an environmental temperature of about 18 C. the hourly insensible loss is approximately 40 centigrams per square decimeter of body surface, whether the subject studied is a small animal, like a guinea-pig, an infant or an adult man. He therefore believes that the insensible perspiration obeys a law comparable to that which governs the expenditure of heat, that the study of the insensible perspiration is accordingly related to the study of nutrition, and that this study may result in new findings in certain chapters in the pathology of the infant and seems capable of certain clinical applications.

In studying the influence of protein and carbohydrate on the heat production in a continuous bath at 37 C., Schmitt [41] in 1925 noted the pronounced effect of protein on the insensible perspiration as compared

39. Meyer, Jean: Revue française de dermatologie et de vénéréologie, April and May, 1925.

40. Meyer, Jean: La perspiration de l'eau chez le nourrisson, Rev. franç. de Pédiat. **1**:409, 1925.

41. Schmitt, W.: Neue Untersuchungen über Eiweisshyperthermie, Jahrb. f. Kinderh. **107**:181, 1925; Weitere Untersuchungen über die Entstehung der "dynamischen Eiweisshyperthermie," Arch. f. exper. Path. u. Pharmacol. **106**:89, 1925.

with that of sugar, the insensible perspiration being almost twice as great, that is, 725 Gm. in six hours with sugar and on the average around 1,700 Gm. with plasmon and meat. No respiration experiments were made. Since the body was in a saturated atmosphere, the absolute values for insensible perspiration may be questioned. It is of importance, however, to note that the author considers the difference in the insensible perspiration as being an indication of the difference in metabolism. The difference between the effect of the ingestion of protein and sugar was noted under identically the same conditions, however, and may be taken as an excellent indication of the well known, striking increase in the metabolism following the ingestion of meat, as compared with that following the ingestion of sugar.

NATURE OF THE INSENSIBLE PERSPIRATION

Based on the literature (not only that cited in this paper but likewise the extensive literature treating of the amount of carbon dioxide lost from the skin, and the water vapor lost from the skin as distinguished from that lost from the lungs) and on a large amount of unpublished material in hand at the Nutrition Laboratory, a general statement with regard to the nature of the insensible perspiration may be made at this point, although experimental treatment of this subject is now being made.

The insensible perspiration deals with the gaseous emanations from the lungs and skin. These emanations are, in the case of human beings, chiefly carbon dioxide and water vapor, for the amount of marsh gas produced is relatively so small that it may be disregarded. Of the carbon dioxide a small amount (approximately 1 per cent of the total) leaves through the skin and the rest leaves through the lungs. The greater proportion (around 85 per cent) of the insensible perspiration, however, is represented by water, vaporized both from the lungs and the skin. Furthermore, the oxygen absorbed by the lungs plays an important rôle in the insensible perspiration. When oxygen is used to burn carbonaceous material, it escapes in the carbon dioxide and obviously is cancelled in the balance between income and outgo. When it is used to burn hydrogen, the water formed may be excreted, but undoubtedly simply goes into the large pool of water in the body. For every gram of hydrogen burned 8 Gm. of oxygen is required, and in this case there is an actual addition to the water of the body, unless one assumes that the water thus produced is immediately lost from the body. On the other hand, when carbonaceous material is burned, the carbon of the carbon dioxide given off represents a true body loss. The innumerable

measurements of human metabolism indicate that the average man or woman, while resting, loses from the body each hour about 6 or 5 Gm. of carbon, respectively, and until further refinement of these values is justified these two figures may be accepted as correct. From an examination of the earlier literature it is obvious that the total average hourly loss in weight ranges from 25 to 40 Gm. The 5 or 6 Gm. ascribable to carbon of carbon dioxide represent, therefore, but a small fraction of the total loss, and the only other factor that enters into the insensible loss to any great degree is that of water. The almost generally synonymous use of the terms "insensible perspiration" and "water vaporized from the body" is thus reasonably justified.

PLAN OF PRESENT RESEARCH

The development in recent years of large respiration chambers, permitting the complete measurement of the gaseous exchange, that is, the determination of the carbon dioxide produced, the water vaporized, and particularly the oxygen consumed, makes it possible to compute the insensible loss indirectly, for the weight of the water vapor given off, plus the weight of the carbon dioxide produced, less the weight of the oxygen absorbed, is essentially the insensible loss from the body. The practical difficulties surrounding the chamber method, the necessity for close confinement of the subject, and the length of time required for the period of observation, led to the attempt to measure the insensible loss by simpler means without undue confinement or restriction. Evidence has been accumulated to suggest that there is a sufficient degree of correlation between the insensible loss and the metabolism to make the measurement of the insensible loss of direct practical value. With this in mind we began our research.[42] The technic was first improved by increasing the sensitivity of the measurements and then shortening the period of observation, so that successive periods of observation could be made and each period used as a control on the preceding one. Finally, the observations were extended into the field of pathology, since relatively appreciable alterations can take place in the metabolism of a pathologic subject, even when resting. Thus, it was possible to study more intimately the correlation between the insensible loss and the metabolism. Evidence of a relationship between muscular activity and insensible loss appears continually in the literature. In the earlier work of the Nutrition

42. Benedict, F. G.: The Correlation Between Perspiratio Insensibilis and Total Metabolism, Collection of Articles Dedicated to the Seventy-Fifth Birthday of Prof. I. P. Pawlow, Published from the Institution of Experimental Medicine in Leningrad, 1924, p. 193; Nouvelle recherches du "Nutrition Laboratory" de Boston sur le métabolisme de l'Homme et des animaux, Bull. Soc. Sc. d'Hygiène Alimen. **11**:343, 1923; Grundumsatz und perspiratio insensibilis nach neuen Untersuchungen, Schweiz. med. Wchnschr. **53**:1101, 1923.

Laboratory and that at Wesleyan University the relationship seemed close. Since the metabolism may be considered as the best measure of muscular activity, and particularly the best measure of vital activity, even when no external muscular work is performed, it was decided that a study of the insensible perspiration and its relation to the metabolism of normal and pathologic subjects, particularly with simultaneous measurements of the metabolism and the insensible perspiration, would be of both physiologic and pathologic importance. This investigation therefore took place in two parts. The physiologic study was carried out at the Nutrition Laboratory. This included the measurements of the insensible loss of a number of normal individuals and subsequently an analysis of the nature of this loss by determining the loss from the skin separately from that from the lungs. The pathologic study was in part carried out by bringing the ambulatory patients to the Nutrition Laboratory and weighing them there on a delicate balance. Subsequently, a delicate balance was installed at the New England Deaconess Hospital, where a large number of pathologic patients also were studied. As the research progressed, the measurement of the metabolism at essentially the same time as that of the insensible perspiration and under the same conditions was also included in the experimental program, whenever possible.

METHODS

Platform Scales.—Preliminary observations were made with platform scales, the so-called "silk scales," such as were used in the researches at Wesleyan University, Middletown, Conn., and at the Nutrition Laboratory with a fasting man. These are manufactured by at least two large scale manufacturing concerns and are designed to weigh about 150 Kg., the scale beam being divided into "10 Gm." divisions. Two forms exist, one with a low and one with a high pillar or post. For convenience in weighing, the high post is preferable. Manufacturers have announced their willingness to supply a traveling weight which would indicate 5 rather than 10 Gm. In figure 1 an illustration of the platform scales is given.

Highly Sensitive Balance.—Although we could not hope to secure a balance having the accuracy and sensitivity of that marvelous instrument perfected at the laboratory of Professor Lombard,[20] we were fortunate in finding a large balance manufactured by August Sauter at Ebingen, Württemberg, Germany. This manufacturer furnishes a number of balances of special construction, the largest of which has a capacity of 100 Kg. on each arm. The Nutrition Laboratory has numerous forms of this balance in several sizes and finds that it is invariably more sensitive and has a larger capacity than the manufacturer

claims. Benedict and Carpenter [43] attached a 100 Kg. Sauter balance to one of the respiration chambers and made it possible to weigh a man suspended on a chair inside the respiration chamber. With this balance it was possible to weigh the subject to within from 0.1 to 0.3 Gm. Since the carbon dioxide produced and the water vaporized were simultaneously measured, it was possible to compute the oxygen consumption indirectly from the actual measurements of the change in body weight, the total water vaporized, and the carbon dioxide produced.[44]

The inherent difficulties of securing a high degree of accuracy when weighing a subject inside a closed respiration chamber and of providing for an air-tight enclosure between the balance and the suspension rod

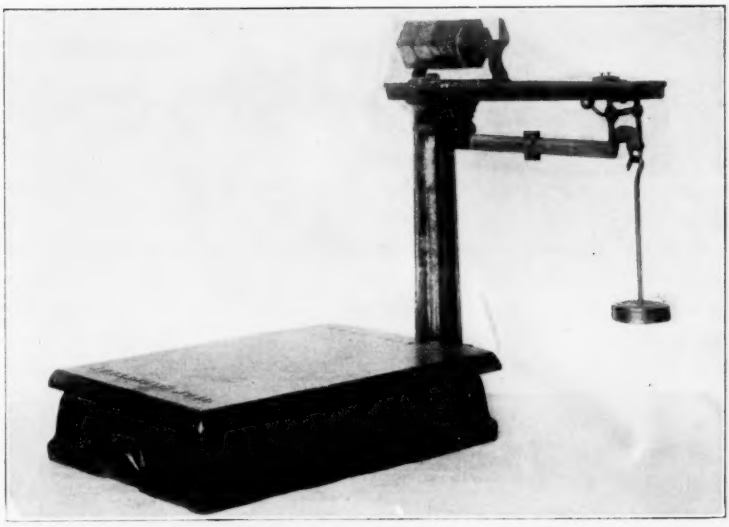

Fig. 1.—Platform scales, so-called "silk scales," sensitive to 10 Gm.

made it impracticable to use this balance for a general study of the insensible perspiration. Subsequently, it was installed in a special room and arrangements were made so that the subject could either sit in a chair or lie on a comfortable suspended spring mattress. Observations therefore began anew on this problem in 1921.[45] The whole apparatus

43. Benedict, F. G., and Carpenter, T. M.: Respiration Calorimeters for Studying the Respiratory Exchange and Energy Transformations of Man, Carnegie Inst., Washington, Pub. no. 123, 1910, figures 4 and 9.

44. Benedict, F. G.: A Comparison of the Direct and Indirect Determination of Oxygen Consumed by Man, Am. J. Physiol. **26**:15 (April) 1910.

45. Benedict, F. G.: Nouvelles recherches du "Nutrition Laboratory" de Boston sur le métabolisme de l'Homme et des animaux, Bull. Soc. Sc. d'Hygiène Alimen. **11**:356, 1923, figure 4.

was demonstrated at the Carnegie Institution of Washington at Washington, D. C., at a conversazione in December, 1923. The successful use of the balance with its suspended spring bed, not only with normal subjects but with a certain number of pathologic cases at the Nutrition Laboratory, made it imperative to install a similar balance in a hospital ward. A second balance was therefore secured from Germany and mounted in the basement of the New England Deaconess Hospital (fig. 2) in the spring of 1925, where often four subjects were weighed in the course of one day.

Obviously, the balance must be well mounted. This has been accomplished by making a rigid support of two upright planks, 12 inches wide, 2 inches thick and about 11 feet long, i. e., 31 by 5 cm. by 3.4 meters. These planks are attached at right angles to each other so as to form a bridge or backbone, and tightly wedged in a true perpendicular position between the ceiling and the floor of the laboratory room. The balance itself rests on a cast iron angle or base, bolted securely to this upright frame. The top of the balance is also fastened to the upright, so that the greatest degree of rigidity is secured and the apparatus is plumb. A fine mesh woven wire cot bed, with the sides turned up from 8 to 10 cm. to hold the bedding securely in place, is suspended on one arm of the balance. On the other arm provision is made for the addition of a large amount of lead or other heavy material as a counterpoise. Finally, a small pan is provided over the bed so that small weights can be added or subtracted quantitatively from this pan. Owing to the large weight suspended (often 200 Kg.) on the balance, it has been found advantageous to raise and lower it by means of a worm gear, the turning of which slowly raises or lowers the balance arm as the operator wishes. Efficiency in its use has been rapidly acquired by a number of untrained workers.

The cooperation of the subject is essential, particularly during the moment when the balance is being suspended and the exact point of equilibrium is being secured. The loss in weight of the body is so continual that it is impossible to secure any exact weight for any stipulated moment. That side on which the bed is suspended is, therefore, slightly overbalanced, and the operator then waits until the loss of weight of the subject equals the weight on the counterpoise, when the time is accurately noted on a watch. From the time between the weighings, as thus noted, and the actual differences in weight, the loss in weight during fifteen minutes or an hour may readily be calculated. Weighings are ordinarily made every ten or fifteen minutes, and from six to twelve weighings secured, which serve as controls on each other.

Both the "silk scales" and the sensitive Sauter balance were selected for the study of the insensible perspiration, since it was believed that

by their use the most normal conditions possible could be secured in the hospital ward. From the standpoint of the patient, therefore, the environment is a normal one, as no confining or restraining appliances are necessary.

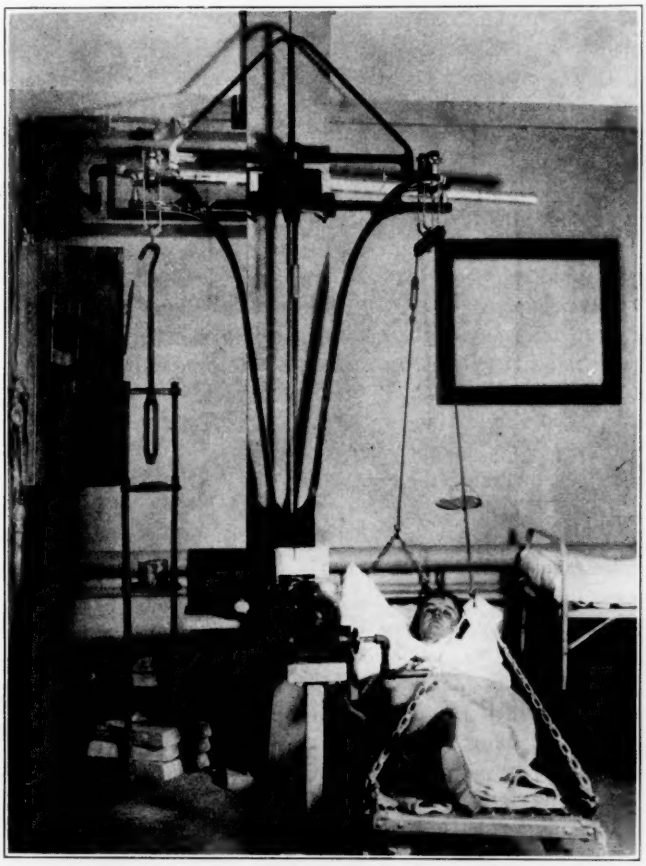

Fig. 2.—Installation of 100 Kg. balance with suspended bed and counterpoise in the New England Deaconess Hospital: the worm gear for raising and lowering is in the foreground; a small circular pan is attached to the support over the bed, and in it are placed weights corresponding to the loss in weight of the subject.

With these two methods equally satisfactory results were obtained. When the silk scales, which have a sensitivity of 10 Gm., are used, the period of measurement is lengthened to cover several hours, so that the total loss in weight will be of such a magnitude that the error in weighing is not significant. Usually an eight or ten hour experiment

is amply sufficient. One difficulty in these long experiments is the possibility of overlooking the slight additions to or deductions from the weight of the body caused by the dropping of a hairpin, the changing of a wrist watch, or even the removal of a set of teeth, as well as by the drinking of water, the taking of medicine, or the passing of urine or feces. If such additions or subtractions are carefully noted, however, and suitable corrections are made in the computation of the true loss in weight, the accuracy is all that could be desired and the method is practicable for a hospital ward. When the silk scales are used, the weight is determined only over one long period, for example, at the beginning of the night and again the next morning. Correction for error in either weight cannot be made, and in order to secure a duplicate value for a check another experiment of approximately eight hours must be made the following night. The advantage in using the balance with a high degree of sensitivity is that the subject is continually under surveillance, from six to twelve weighings are secured in a relatively short time, and an aberrant weight is instantly noted if the values for the weights are plotted in relation to the time. Obviously the cost of the "silk scales" is small, amounting to thirty or forty dollars. The balance will cost approximately $200, and the labor of mounting it with worm gear perhaps another hundred dollars, depending on the skill of the person mounting the apparatus.

RESULTS

Preliminary Overnight Experiments with Platform Scales.—Although the experiments with these scales (sensitivity 10 Gm.) at Wesleyan University indicated that results of value could be obtained with them, further tests of the method were made by a member of the laboratory staff (T. M. C.) and his wife (K. M. C.) in intermittent observations at their home during a period covering the greater part of a year. The subject, T. M. C., who weighed 53.5 Kg., found as an average of thirty weighings during periods at night of eight hours each, that his hourly insensible loss was 27.4 Gm. The normal woman, K. M. C., whose average weight was 60 Kg., had for sixty-four nights an average hourly insensible loss of 28.7 Gm. The variations from these average values were occasionally large, but since the balancing of the scale arm and reading of weights were uncontrolled, the results may be considered to be reasonably uniform. When the readings are unchecked, however, it is only the general picture of such preliminary observations that can be considered. To be accurate, the weighings should obviously be made by another person, as it is difficult for the subject to adjust the balance when squatting down, and still more difficult to read it accurately.

A second series of overnight weighings with the platform scales was made by the normal subjects H. K. R. and H. F. R. and gave more uniform results. The average loss of the woman, H. K. R. (average body weight 55.5 Kg.), during five consecutive nights amounted to 24 Gm. per hour, with great regularity from night to night. Prior to this series measurements on another set of scales, which were unsatisfactory, showed great variability in the loss of weight and also larger losses, averaging 30 Gm. per hour. In this series, however, the subject had taken a warm bath each night just prior to the weighings. It is reasonable, therefore, to believe that the skin was surcharged with water and that the larger loss noted on these nights was due to the effect of the bath. The man, H. F. R. (average body weight 74.5 Kg.), had an average loss of 29 Gm. per hour on four different nights.

The only conclusions to be drawn from these preliminary overnight observations on normal subjects are that in general the loss is approximately proportional to the body weight and that with extra precautions fairly uniform values on successive nights can be secured.[46] In the earlier observations of F. G. B. and C. G. B.[47] it was noted that on those nights when the subjects slept very quietly the loss was much less than on nights when there was considerable restlessness. This fact would indicate that muscular activity results in a larger loss.

On the basis of these preliminary experiments this method was put into use at the New England Deaconess Hospital, but special care was taken to adjust the balance beam accurately at each weighing, to read the weights carefully, to take an inventory of the clothing and other appurtenances worn at the time of the initial weighing, to record the time and amount of any intake of drink or food and any passage of urine or feces, and to make sure that the clothing was the same at the time of weighing on the following morning. Under these conditions, particularly when the situation was not complicated by the drinking of water or the passing of urine, an extensive series of observations was made at the hospital on thirty-two diabetic patients. Duplicate experiments,

46. The significance of these overnight experiments was pointed out by one of us in a lecture at the University of Hamburg in June, 1923, and Professor Kestner, with characteristic energy, immediately had a number of balances placed in different wards of the hospital. The next day, however, he stated that their observations had failed to confirm the prediction of a general correlation between insensible loss and body size, the simplest index of metabolism. This was somewhat surprising, since Professor Kestner himself had made very practical use, in studies on the water balance in the body, of determinations of the loss overnight, and had reported an interesting series of nine to ten hour overnight losses, ranging in his own case from 211 to 360 Gm. (Sohnheim, O.; Kreglinger, and Kreglinger: Beiträge zur Physiologie des Wassers und des Kochsalzes, Ztschr. f. physiol. Chem. **63**:420, 1909).

47. Benedict, F. G., and Joslin, E. P.: A Study of Metabolism in Severe Diabetes, Carnegie Inst., Washington, Pub. no. 176, 1912, p. 91.

usually on consecutive nights (in one instance five nights), showed a singular uniformity in the loss of weight per hour.

SHORT EXPERIMENTS WITH A HIGHLY SENSITIVE BALANCE

It was essential at the outset to study two important problems, i. e., whether the insensible loss in weight is regular from night to night and whether it is regular from hour to hour. Obviously only the first of these questions could be answered by overnight measurements. But to determine the regularity in the hourly loss it was necessary to employ a highly sensitive balance, which would permit from six to ten accurate measurements during a period not of eight hours but of one hour or two hours. The large, sensitive Sauter balance was therefore mounted in a special room in the Nutrition Laboratory in the fall of 1923, and various members of the laboratory staff were weighed in periods varying in length from thirty minutes to an hour, at intervals of about ten minutes.

FACTORS AFFECTING THE "PERSPIRATIO INSENSIBILIS"

During the observations in 1923 factors which are now known to have a pronounced influence on the insensible perspiration were, through ignorance, entirely disregarded. Thus, the influence of the character and the amount of food eaten prior to the test and the length of time that elapsed following the meal were ignored. To be sure, precautions were taken not to make experiments on rainy or snowy days when the subject's clothing, particularly the shoes and stockings and the lower part of the trousers or skirts, would be wet. But it is undoubtedly true that in certain instances the face and hands had been washed and the hair had been wet just prior to the tests, for the members of the staff were frequently called from their regular work at almost any hour of the day to serve as subjects on the balance for one or two hours. The after-effect of climbing the three flights of stairs to the room where the balance was installed, and any psychical effect (these being especially to be found in pathologic cases) were also too often overlooked. Thus, the data were secured under conditions that could not at the present day be considered as ideally comparable.

Body Size and Sex.—The values for the insensible loss of these normal subjects, as noted in experiments lasting from thirty minutes to two hours, are tabulated in table 2, in the order of increasing body weights. An inspection of this table shows that in general the smaller body weight is accompanied by a small insensible loss, and that the largest insensible losses occur with those subjects having the largest body weights. Another factor, however, should be considered in the interpretation of these figures, i. e., the possible influence of sleep, since unavoidably in some instances the subjects were asleep. The losses

recorded in this table may therefore be affected by the factors of food, sleep, exercise, psychic apprehension and moisture on hair, hands and face, and for this reason the only definite conclusion that can be legitimately drawn from these data is that in general the larger insensible loss occurs with the larger body weights.

Food.—In all the measurements reported in table 2 the subjects were quiet but had eaten food. Since it was known that food and changes in body position or slight muscular activities result in an increased metabolism, preliminary observations were made with normal subjects on the influence of these factors on the insensible loss. From the data in table 3 it is obvious that following the ingestion of food (amount and character of food not recorded) there is invariably an increase in the insensible loss.

TABLE 2.—*The Insensible Perspiration of Normal Persons During the Day*

Subject*	Body Weight (Nude), Kg.	Insensible Loss per Hour, Gm.
1	36.5	19.5
2	42.5	21.0
3	44.5	18.0
4	48.5	19.0
5	50.5	28.5
6	52.5	30.5
7	59.3	28.5
8	60.0	22.0
9	60.0	28.0
10	60.3	20.0
11	62.0	28.5
12	63.1	36.0
13	63.3	32.5
14	66.0	30.0
15	67.2	30.0
16	73.3	26.0
17	78.9	30.0
18	77.2	29.5
19	89.0	33.0
20	90.5	44.0

* Subjects 2, 3, 4, 8 and 10 were women; all the others were men.

Exercise.—The effect of moderate exercise involving a change in position from lying to sitting, and the effect of more vigorous exercise, such as walking, calisthenics or riding on a bicycle ergometer, were also studied with normal subjects. In a series of experiments with seven subjects, in which the influence of a change in position from lying to sitting was studied (unfortunately the two positions were studied on different days), an increment in the insensible loss when the subject was sitting was invariably noted. This increment amounted generally to about 5 Gm. per hour. In the case of two men who walked vigorously around the room for ten minutes, the loss (computed on the hour basis) rose from 33 Gm. while the men were lying quietly, to approximately 60 Gm. A woman, who exercised in calisthenics for fifteen minutes, increased her insensible loss from 25 Gm. per hour (lying) to 43 Gm. In a few experiments in which a subject rode a bicycle ergometer

vigorously until visible perspiration appeared, there were very great increases in the loss, amounting to 500 and 600 per cent, or even more. Since, however, the plan of this research was to study the insensible loss prior to the onset of visible perspiration, the details of these experiments with the bicycle ergometer are reserved for later publication.

RELATIONSHIP BETWEEN "PERSPIRATIO INSENSIBILIS" AND METABOLISM

The conclusion that there is a general tendency for the insensible loss to be greater with larger weights and with increasing activities, coupled with the fact of the well known relationship between body size, body activity and metabolism, immediately suggested the possibility of a relationship between the insensible loss and the metabolism. To determine whether such a relationship exists it would be ideal to carry out a series of observations on normal subjects which should include the measurement of the insensible perspiration and immediately thereafter the measurement of the basal metabolism. Few normal subjects were studied in

TABLE 3.—*Influence of Food on the Insensible Perspiration of Normal Subjects*

Subject	Loss per Hour	
	Before Food, Gm.	After Food, Gm.
Men		
7	28.0	32.4
14	27.3	34.6
15	33.0	36.5
17	29.5	33.4
19	34.4	39.0
Women		
2	20.9	24.4
8	16.8	21.2

this way, however, for it became possible, thanks to the cooperation of Drs. E. P. Joslin and F. H. Lahey, to make this comparison with diabetic and thyroid patients at the New England Deaconess Hospital. Because of the marked difference between the metabolism of the diabetic patient, whose chief object in life is to conserve heat, and the metabolism of the toxic goiter patient, whose chief object in life is to lose heat, it was believed that a series of observations on these two types would furnish the best evidence as to the possible relationship between insensible perspiration and metabolism. Accordingly, a relatively large number of both types of patients were studied, and the loss in weight was measured just prior to the determination of the metabolism.

In figure 3 are plotted the results of such measurements on the diabetic and thyroid patients, the insensible perspiration (expressed as grams per hour) being represented by the ordinates and the heat production for twenty-four hours (as computed from the determined oxygen

consumption) by the abscissas. The thyroid patients are indicated by dots and the diabetic patients by small crosses.

Although the scatter of the plotted points makes the laying on of a straight line curve debatable, nevertheless since it is not materially greater than the scatter in many charts in which curves have been drawn for the prediction of the metabolism, such a curve has been drawn in figure 3 in accordance with the custom of the Nutrition Laboratory in preparing smoothed curves.[48] This curve shows that there is a reasonably close relationship between the insensible perspiration and the measured metabolism.[49] As is to be expected, the diabetic patients have in general the lower metabolism, the crosses representing the diabetics being, with few exceptions, at the lower, left hand side of the chart. The numerical scatter of the crosses above and below the straight line is essentially uniform. The dots representing the thyroid patients extend to the upper part of the curve, indicating their great heat production. The comparison made in figure 3 obviously does not introduce the element of size (either height, weight or surface area) or of age, for the problem is to note whether there is any correlation between the loss of weight and the production of heat, irrespective of the size of the subject.

INFLUENCE OF ENVIRONMENTAL TEMPERATURE OR SKIN TEMPERATURE

In this series of observations aberrant figures were not infrequently found, especially with the thyroid patients, and the protocols showed that in such instances there was invariably visible perspiration. These data were not plotted in the chart. In a number of cases it was also observed that the points lying well below the line, toward the outer scatter, represent experiments in which the temperature of the room or the prior exposure of the subject was such as to lead to the belief that the subject was *cold*. Here for the first time was the significant influence of environmental temperature clearly recognized.

48. Benedict, F. G.: Physical Factors in Predicting the Basal Metabolism of Girls, Proc. Am. Philosophical Soc. **63**:31 1924.

49. Belief in the relationship between insensible perspiration and metabolism is strongly supported by the striking observations of Prof. E. G. Ritzman of the Institute of Animal Nutrition at the University of New Hampshire. In his experiments it has been found that when the insensible perspiration and simultaneously the metabolism of adult steers (weighing 600 Kg.) are carefully determined, changes in the insensible perspiration are closely related to changes in the total metabolism. Thus, a large steer on full ration, producing about 16,000 calories per day, had an insensible perspiration of approximately 16 Kg. After a period of prolonged submaintenance feeding, when the animal had adjusted itself to its lower nutritive plane and the metabolism had fallen to approximately 8,000 calories per day, the insensible perspiration was not far from 6 or 7 Kg. per day.

Most of the studies on normal subjects had shown seemingly little, if any, influence of environmental temperature on the insensible perspiration. Indeed, the act of disrobing and subjecting the body to a blast of room air from a strong electric fan frequently did not alter in the slightest the insensible loss. A series of experiments was then planned with normal subjects, to study simultaneously the insensible perspiration and the metabolism, first, when the environmental temperature was low (16 or 17 C.), then when the temperature was increased 5 degrees, and again when it had been increased still another 5 degrees. Under these conditions the subject was at the start of the experiment cold, or, in the last analysis, the actual skin temperature was low. Thus, this

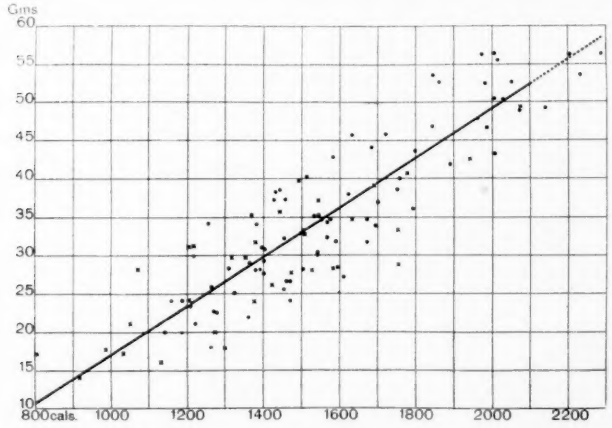

Fig. 3.—Relationship between the insensible perspiration per hour and the simultaneously measured heat production per twenty-four hours of a group of diabetic and thyroid patients: the diabetic patients are indicated by crosses and the thyroid patients by dots; the straight line curve representing the general trend of the points is suggested as a method for predicting probable metabolism from measured insensible perspiration.

series of experiments dealt immediately not so much with the influence of environmental temperature as with the influence of the skin temperature at the time of noting the insensible perspiration. The results of these experiments showed that there was no material alteration in the metabolism or in the loss of weight of the men subjects, there being only a slightly greater loss of weight at the highest temperature (26 C.) than at the lowest temperature (16 C.). On the other hand, the preliminary cooling to which the women were subjected during the first hour and a half (at an environmental temperature of 16 C.) was so great that in the subsequent periods of increased environmental temperature it was impossible to raise the skin temperature to approximate that which would normally be expected after a night's repose in bed, under bed

clothing. Hence the insensible loss, as measured, was always much lower than would be expected from the curve in figure 3.

When the loss in weight and the metabolism of members of the Nutrition Laboratory staff (i. e., normal subjects) were simultaneously measured, it was found that in many instances their insensible perspiration was much lower in relation to their metabolism than would be expected from the curve given in figure 3. A survey of the skin temperature at six various points under the clothing and on the face and forehead showed that the skin temperature was cold. By warming up the room and by covering the subject with more blankets, there was an increase in the loss of weight, accompanied by an increase in the skin temperature. In the case of the normal women subjects it was noted that the scanty modern attire resulted in a cold skin temperature, particularly on the extremities. Only when they were well protected with blankets and the skin temperature had attained that point which would be reached after a night's rest in bed, was the insensible loss at all comparable to that of the men subjects, who are usually much more warmly clad than are women. An experiment was therefore made, designed to test out this particular point as to the influence of differences in protective clothing. One of the women subjects was liberally wrapped in blankets, both under and over her, and long socks were drawn over the feet and legs. By this means her skin temperature was made to approximate that which would obtain if she had been lying in bed, but care was taken to avoid overheating and the possibility of visible perspiration. Under these conditions the insensible loss, when referred to the total metabolism simultaneously measured, was exactly that predicted by the slope of the line given in figure 3.

In this connection it is interesting to point out that evidence has been furnished by Viale,[50] which indicates that, in accordance with a hypothesis of Galeotti, not only is the cutaneous circulation affected by a cold skin temperature but likewise the pulmonary circulation. Thus, Viale finds that as a result of a cold skin temperature the temperature of the expired air falls perceptibly, which would of itself lower the amount of water brought out by the expired air.

IDEAL CONDITIONS FOR MEASUREMENT

From a practical standpoint no one would think of measuring a hospital patient in a room at a temperature of 16 C. or when the skin temperature was very low. On the other hand, experiments made under conditions resulting in the appearance of visible perspiration are, at least until further experimental evidence is forthcoming, ruled out.

50. Viale, G.: Rapporti tra la temperatura dell' aria espirata e la temperatura cutanea, Arch. per le sc. Med. **43**:40, 1920; Rapports entre la température de l'air expiré et la température cutanée, Arch. ital. de biol. **72**:32, 1923.

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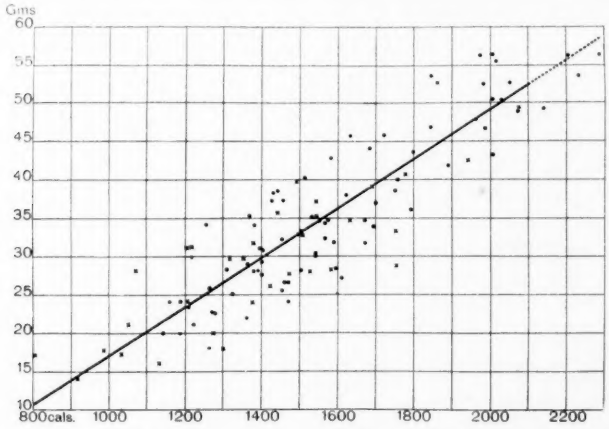

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At 26 C., for example, it is not unlikely that there may be visible perspiration, certainly with thyroid patients and with some normal subjects. It is believed, therefore, that the ideal conditions for the measurement of the insensible perspiration require that the subject should be lying, comfortably warm, either clothed and preferably covered with one or more thicknesses of blanket, or in bed with sufficient bedding to insure that the hands and feet are not cold and yet the subject does not feel so warm that visible perspiration is induced. Light moisture at the armpits probably does not affect the results. One should look for perspiration not only on the palms and face but also on the back, where contact with the bed may cause sweating. Under these conditions an environmental temperature of not far from 23 C. will be found satisfactory. Measurements may undoubtedly be made at temperatures below 23 C., if the subject has more covering, but above 26 C. (perhaps even with no blankets covering the subject) visible perspiration may be expected and should be looked for by the experimenter. Ordinary bed clothing will be all that is necessary for bedridden patients.

We are convinced that many of the deviations from the straight line curve exhibited in figure 3 may well be explained by the actual environmental temperature at which the experiments were made, or, more properly speaking, by the skin temperature, extremely low values for loss in weight unquestionably being explainable by low temperatures. It is realized that skin temperature measurements are not as yet possible in all clinics, although the apparatus is extremely simple and may be generally afforded.[51] Means [52] has shown that variations in the metabolic rate are accompanied by variations in the rate of blood flow. Thus, in muscular work and in hyperthyroidism the increase in rate of blood flow nearly parallels the increased metabolism. The loss of water vapor from the skin would seem to depend in part on the rate of blood flow under standard conditions of environmental temperature.

NORMAL CONTROL MEASUREMENTS

To control the accuracy of the suggested relationship between the loss in weight and the metabolism it is essential that both be measured at the same time or at essentially the same time. This requirement, however, immediately makes questionable the comparison of the loss overnight (determined on the silk scales) with the metabolism measured the next morning. Experiments in which the loss has been measured overnight on the silk scales and again the next morning on a more

51. Benedict, F. G.; Miles, W. R., and Johnson, A.: The Temperature of the Human Skin, Proc. Nat. Acad. Sc. **5**:218 (June) 1919; Benedict, F. G.: Die Temperatur der menschlichen Haut, Asher-Spiro's Ergebn. d. Physiol. **24**:595, 1925. (Sold by W. E. Collins, 584 Huntington Ave., Boston.)

52. Means, J. H.: Circulatory Disturbances in Diseases of the Glands of Internal Secretion, Endocrinology **9**:192 (May) 1925.

sensitive balance, with a simultaneous measurement of the metabolism, indicate that the factors affecting the loss overnight may have a compensating effect. Thus, the metabolism in the early evening is somewhat elevated due to the after-effects of the evening meal. Deep sleep results in a decreased metabolism, and the awakening in the morning again causes an increased metabolism. It is therefore probable that the metabolism measured after a weighing period in the morning closely approximates the average metabolism for the entire night, and it is believed that if the weights on the silk scales are carefully made, they are of equal value with those measured on delicate scales.

The control of the slope of the straight line curve in figure 3 with normal data is not simple, for although it is easy to secure members of the laboratory staff, i. e., normal persons, having a moderately low metabolism, persons having a basal heat production of 2,500 calories are not common. However, fourteen normal persons have been studied under the ideal conditions stipulated above and their measurements (essentially simultaneously determined) lie close to this line. Hence we feel justified in proposing, tentatively, a straight line curve of the order of that shown in figure 3 for use in comparing the *measured* insensible perspiration under the conditions stipulated with the *probable* metabolism at the time of measurement. With the accumulation of further data we are quite prepared to look for a slight change in the slope of this line. Indeed, our own experience with normal subjects has led us to believe that the inclination of the upper (broken) part of the line may perceptibly decrease. With at least one normal subject, whose hourly loss in weight was 50 Gm., the tendency has been for the plotted point indicating the relationship between the insensible perspiration and the measured metabolism to lie somewhat below the line, at about 2,400 calories. In this case, however, the metabolism is even higher than would be predicted by the curve. A possible explanation of this discrepancy between the normal data and the thyroid data at this upper part of the curve may be that with thyroid patients the proportion of water lost from the lungs and from the skin, which apparently is fairly regular up to 45 or 50 Gm., may be disturbed, due to the higher vascularity of their skin and that visible perspiration may be about to break out. The thyroid and the normal subject might have the same metabolism, and yet the skin of the thyroid patient might be hotter and more moist than that of the normal subject and thus more water would be given off from the skin. When the hourly loss in weight reaches about 50 Gm. or over, therefore, the probabilities are that the predicted metabolism, based on the curve in figure 3, will be for normal individuals low rather than high.

In a direct comparison of the loss in weight and the metabolism it is important to emphasize that the subject should be more or less

accustomed to metabolism measurements, for with an apprehensive subject a psychic disturbance may occur which will result invariably in too high a metabolism (as a rule the measured metabolism is rarely, if ever, *below* basal). Indeed, it should be pointed out that the subjects studied in connection with the data plotted in figure 3 were not apprehensive. They had become accustomed to having their metabolism measured frequently, in some cases daily. Likewise, the patients were in all instances in the hospital on the night previous to the measurements and therefore had not undergone the excitement and exertion of a journey to the hospital without breakfast.

PRACTICAL USE OF MEASUREMENT OF INSENSIBLE PERSPIRATION IN PREDICTING METABOLISM IN LABORATORY AND CLINIC

In the practical use of this curve the metabolism may be predicted from the insensible perspiration accurately measured either on a delicate balance during a period of from one to two hours or on the silk scales for a period of from nine to ten hours, the loss per hour being computed at the end of the period of measurement. It is immaterial whether the subject is in a basal condition or whether the measurements are made after the ingestion of food, whether they are made during a moderate amount of regular exercise or, indeed, during fever. We have every reason to believe that the loss as thus accurately measured predicts with reasonable correctness the metabolism *obtaining at the time the loss in weight was determined*, but not during any other period. Thus, the loss when the subject is lying quietly, without food in the stomach and without fever, may not be referred to the metabolism after the subject has had food or has a febrile temperature.

To use this chart, however, for the practical purpose of giving a clue as to the probable *basal* metabolism, it is obvious that the measurements of the loss in weight should be made not only under the conditions outlined above, but likewise under the conditions ordinarily required for basal metabolism measurements, that is, during complete rest and with the subject in the postabsorptive condition, or about twelve hours after the last meal. To insist on the postabsorptive condition is practical when the measurements are made in the hospital on an accurate balance, which will permit measurements over a short period of time. On the other hand, when the measurements are made overnight on the silk scales, it would be somewhat of a privation to submit the subject to a twelve hour fast prior to the evening weighing and then not allow him food until the next morning after the final measurements are made. Under these conditions a light supper at 6 p. m., containing a minimum of ketose sugar, such as levulose or sucrose, is permissible. The insensible perspiration thus measured, when referred to the curve in figure 3, will

give a clue as to the probable basal metabolism. By likewise predicting the subject's basal metabolism from the normal standards based on the characteristics of the individual (age, sex, height, weight or surface area), one can note whether or not the metabolism as predicted from the insensible perspiration is higher or lower than that predicted for the average subject of like physical characteristics. Thus, if the subject has a loss in weight of 25 Gm. per hour, determined when there is no food in the stomach and when there is no undue activity, he should have a basal heat production of not far from 1,250 calories for twenty-four hours. If the loss in weight is measured under basal conditions, it is proper to refer this heat production of 1,250 calories to the metabolism predicted from any of the standards commonly used, taking into consideration age, sex, height and weight (as is done by Harris and Benedict [53]) or age, sex and surface area (as is done by Du Bois [54]).

The error in the prediction of the metabolism from the insensible loss by this curve has not been calculated, for as yet the number of persons who have been measured with scrupulous care is very small. Certainly the error of prediction may not be computed for the individual points given in figure 3 for, as already stated, it is probable that with more careful attention to the control of the environmental temperature and other details, such as not washing the face and hands and not wetting the hair, many of these deviations would disappear. With the accumulation of further simultaneous measurements of metabolism and insensible loss, the material for the computation of the error of prediction will be at hand. On the basis of the data available at present it can only be stated that between the insensible perspiration (measured under the conditions outlined above) and the simultaneously measured metabolism there is a relationship and that this relationship is sufficiently close to permit the use of the insensible perspiration as a general index of the probable metabolism of a subject. It is obvious that this method of approximating basal metabolism can never replace the accurate, painstakingly recorded basal metabolism measurements under "standard" conditions. The weighings overnight are simple, however, and add but an insignificant expense to the hospital care of the patient, and the general trend of the curve in figure 3 is such that it is believed that it will be helpful in the preliminary assessment of the metabolic condition of many patients.

To simplify the use of this curve, the values for the probable metabolism as predicted from the hourly insensible perspiration at 2 Gm. intervals from 14 to 58 Gm. are given in table 4.

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53. Harris, J. A., and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man, Carnegie Inst., Washington, Pub. no. 279, 1919.

54. Aub, J. C., and Du Bois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. **19**:831 (May) 1917.

A relationship seemingly as close as that found in these experiments between the insensible perspiration measured under carefully controlled, standardized and reproducible conditions and the metabolism existing at the time of measurement may have important bearing in the clinic. Indeed, as early as 1869 von Leyden made use of measurements of insensible perspiration in studying fever, and subsequently Schwenkenbecher and Inagaki, Isenschmid, Krehl, Nobel and Meyer also made clinical use of this measurement. These investigators, however, were chiefly concerned in the water balance, a phase of metabolism which has only too slowly been given serious attention but which today is interesting a large number of physicians.

The determination of the insensible perspiration has already been found clinically useful at the New England Deaconess Hospital, in giving an approximation of the metabolism under conditions of natural rest,

TABLE 4.—*Twenty-Four Hour Heat Production of Human Beings Predicted from the Insensible Perspiration per Hour*

Insensible Perspiration Gm.	Predicted Heat Calories	Insensible Perspiration Gm.	Predicted Heat Calories
14	900	38	1,655
16	965	40	1,715
18	1,028	42	1,775
20	1,090	44	1,840
22	1,155	46	1,900
24	1,215	48	1,965
26	1,280	50	2,025
28	1,345	52	2,085
30	1,405	54	2,145
32	1,470	56	2,210
34	1,530	58	2,275
36	1,590	..	.....

undisturbed by the physical inconvenience of mask or mouthpiece or by the psychical stimulus of the "laboratory test." In the accumulation of the pathologic data plotted in figure 3 numerous opportunities occurred to study the relationship between the metabolism and the insensible loss when there were great changes in the metabolism in the same individual. Thus, in several cases of toxic goiter it was noted that both the insensible loss and the metabolism were very high prior to operation but that following operation both decreased and, indeed, in reasonably close proportion. It would appear, therefore, as if the insensible loss might be of significance in indicating the lowering of metabolism following a goiter operation.

The following cases are also cited as examples of the clinical value of the measurement of the insensible perspiration.

REPORT OF CASES

CASE 1 (no. 3700).—Mrs. B., aged 50, who weighed 57 Kg., with a height of 158 cm., had lost 14 Kg. in six months, in spite of an apparently normal caloric intake. She had extreme nervous symptoms and was referred to the hospital by

an excellent internist as having a possible case of hyperthyroidism. Nov. 10, 1925, a basal metabolism determination, the first she had ever had, indicated that her twenty-four hour heat production was 1,732 calories, or 38 per cent above normal by the Harris-Benedict standard. November 15, her insensible perspiration at night, during nine hours in bed, was 32.7 Gm. per hour. On the basis of our study of the relationship between metabolism and insensible perspiration it was believed that this measurement almost surely proved that this was not a case of true hyperthyroidism (or an elevated basal metabolism), but that the element of apprehension and psychic disturbance was responsible for the abnormally high metabolism. Fortunately it was possible to check the metabolism determinations on two other occasions. Thus, November 16, her basal twenty-four hour heat production was 1,424 calories (13.5 per cent above normal) and, November 17, it was 1,410 calories (12 per cent above normal). Dr. F. H. Lahey examined the patient and considered that no hyperthyroidism was present. This patient was extremely nervous and it was difficult to measure the metabolism satisfactorily. The experience in her case illustrates what is believed to be true, namely, that a single determination of the insensible perspiration *carefully* made may be more useful clinically than a *single* measurement of the basal metabolism by the ordinary methods.

TABLE 5.—*Measurements of Basal Metabolism and Insensible Perspiration in Case 2*

Date	Heat Produced per 24 Hours, Calories	Deviation from Harris-Benedict Standard,* per Cent	Insensible Perspiration per Hour, Gm.	Radial Pulse
December 23	1,626	+44	....	...
December 24	.....	....	38.6	100
December 26	1,522	+35	44.2	152
December 29	1,466	+31	35.3†	112
December 30	1,612	+47	....	...

* Based on actual weight on day of metabolism experiment.
† Asleep in this test.

In a second instance the measurement of the insensible perspiration gave valuable support to the diagnosis of hyperthyroidism.

CASE 2.—Mrs. H., aged 72, whose weight was 52 Kg., with a height of 152 cm., entered the New England Deaconess Hospital for treatment of "eczema," which was supposed to have been brought on by the taking of potassium iodide (about 1 Gm. per day) for fifteen months. Previous to taking the potassium iodide she had been nervous, had lost weight, and had had paroxysms of rapid heart action. The potassium iodide treatment had been followed by a gain in weight and improvement in heart action, but by little change in nervousness. On examination it was found that she had auricular fibrillation with an apex rate of 156, which was not affected by small doses of digitalis. She became nauseated after a few doses of digitalis by mouth and could not retain it by rectum. Direct examination showed very slight thyroid enlargement, slight eye signs, and tremor. Several measurements of both the basal metabolism and the insensible perspiration gave the results tabulated in table 5. Her extreme nervousness and discomfort while wearing the mask made interpretation of the high metabolism figures a little uncertain, especially in view of her age, the slight physical signs and her recent gain in weight. However, the constantly high insensible perspiration aided in making a diagnosis of hyperthyroidism, since it ruled out the possibility of the elevation in metabolism being due to nervousness, induced by the wearing of the mask and the sense of suffocation it produced in her.

The measurement of the insensible perspiration in a third instance gave information regarding the metabolism of a man too ill to wear any sort of face mask or mouthpiece.

CASE 3 (no. 169).—A man, aged 68, whose weight was 67 Kg., with a height of 170 cm., had had diabetes for eighteen years. Gangrene had necessitated the amputation of a leg two years previously. At the time in question he was admitted again to the New England Deaconess Hospital because of prostatic obstruction. He refused to continue a catheter existence and, in spite of the known risk, insisted on operation. Following a suprapubic cystostomy he became apathetic and mildly uremic, developed edema, and for weeks would eat nothing voluntarily. Intravenous injection of glucose, feeding by stomach tube, and rectal feeding were resorted to, until he resisted them all.

The striking feature of his case was the absence of ketosis, in spite of almost complete fasting. The amount of caloric intake is uncertain, because of vomiting. The food taken intravenously was the only food definitely to be estimated in the caloric intake, for even the food given per rectum was not always retained. However, for nine days his daily food intake had not exceeded 8.5 Gm. of carbohydrate, 2 Gm. of protein and 5 Gm. of fat. It seemed likely that a low metabolism (in spite of a pulse rate around 90) might account for the absence of ketosis. His insensible perspiration was found to be 14.4 Gm. per hour, an extremely small loss for a person of his weight, indicating a greatly depressed metabolism.

This case illustrates the value of the measurement of the insensible perspiration in making possible an approximation of the metabolism when, for practical reasons, the ordinary methods of determining the metabolism may not be employed.

SUMMARY

The significance of the loss in weight due to invisible, gaseous emanations, chiefly water vapor and carbon dioxide, or the so-called "perspiratio insensibilis," was recognized as early as 1614 by Sanctorius. Since that time measurements of this loss have occasionally been used in the clinic, chiefly as an aid in indicating variations in the water balance in the body.

In the research reported in this paper two methods were employed for studying the insensible perspiration. With platform scales, sensitive to 10 Gm., the insensible loss was determined overnight during a period of nine or ten hours, thus enabling the calculation of the hourly loss with an accuracy of approximately 5 per cent. An extremely sensitive balance, capable of weighing 100 Kg. with an accuracy of 0.1 Gm., has also been used for measuring this loss in successive periods of from ten to fifteen minutes' duration. Measurements by these two methods indicate that in general the larger individual has the larger insensible perspiration.

Refinement in the method of measurement brought out sharply the influence of body size, ingestion of food and exercise on the insensible loss. Since these factors likewise affect the metabolism, it is evident

that there is a relationship between the insensible loss and the metabolism. Thyroid patients, whose metabolism is high, were found to have a large insensible loss, and diabetic patients, whose metabolism is low, were found to have a small loss. The relationship between the insensible perspiration and the metabolism of these two types of pathologic cases was such that when the data for the hourly insensible perspiration were plotted with reference to the twenty-four hour heat production, a straight line curve indicated the general trend of the metabolism.

The ideal conditions for measuring the insensible perspiration so that the data may be used for comparative purposes require that the body should be warm and comfortable, and that the extremities, particularly in the case of women, should be well protected. This fact was brought out when it was noted that the environmental temperature, which profoundly affects the skin temperature, plays a decided rôle in the insensible loss. When the insensible perspiration of either pathologic patients or normal subjects (workers in the laboratory) was measured under these ideal conditions and the metabolism was determined at essentially the same time, it was demonstrated that the straight line curve based on the data for diabetic and thyroid patients may serve as an excellent index of the metabolism obtaining at the time of measurement of the insensible perspiration, even with normal subjects.

Table 4 indicating the expected twenty-four hour heat production for insensible losses in weight of from 14 to 58 Gm. per hour, at intervals of 2 Gm., shows that if the insensible loss is known, the probable metabolism can be readily approximated.

Practical use of this method in the clinic has already demonstrated its helpfulness.

THE RATE OF UREA EXCRETION AS A TEST OF RENAL FUNCTION BY MEANS OF A MODIFICATION OF McLEAN'S INDEX *

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Although hitherto there have been several methods for testing renal function, few of them indicate accurately the ability of the kidney to excrete waste and metabolic end-products. The concentration and dilution tests are practical, and applicable for clinical purposes. It is possible to test the ability of the kidney to excrete foreign substances, such as phenolsulphonphthalein, lactose, potassium iodide and indigo carmine, but no one test will give equally satisfactory information in all cases of renal insufficiency, and the result differs according to the type of case. In a study of the elimination of substances normally excreted by the kidney the estimation of nitrogen, urea, chlorides and so forth, following the ingestion of an analyzed or calculated diet must be considered. The micromethods of Ivar Bang, the system of blood analysis of Folin and Wu, and the investigations of V. C. Myers are valuable in the determination of the concentration of the metabolic products in the blood. In 1915, McLean [1] introduced an index based on Ambard's law, which was designed to show the rate of urea excretion. At present the urea in blood and urine is estimated, the urine is measured, the body weight determined, and the index calculated from the following formula.[2]

$$\text{Index} = \frac{\text{Grams of urea for each twenty-four hours gram } \sqrt{\text{urea for each liter of urine} \times 8.96}}{\text{Weight in kilos} \times (\text{grams of urea for each liter of blood})^2}$$

This test is especially convenient since it obviates the necessity of keeping the patient's diet constant. McLean [3] could take 10 cc. of blood without injury to the patient, but the micromethod used in this study requires only 0.4 cc. of blood. A short report is presented here of observations made on patients in the clinic.

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* From the medical clinic of Prof. Dr. K. Miura, Imperial University of Tokyo.

1. McLean, F. C.: The Numerical Laws Governing the Rate of Excretion of Urea and Chlorides in Man: I, An Index of Urea Excretion and the Normal Excretion of Urea and Chlorides, J. Exper. Med. **22**:212-236, 1915; II, The Influence of Pathological Conditions and of Drugs on Excretion, ibid. **22**:366-388, 1915.

2. McLean (Footnote 1, second reference).

3. McLean, F. C.: Clinical Determinations of Renal Function by an Index of Urea Excretion, J. A. M. A. **66**:415-420 (Feb. 5) 1916; The Mechanism of Urea Retention in Nephritis, J. Exper. Med. **26**:181-199 (Aug.) 1917.

METHOD OF EXAMINATION

As a rule this procedure requires a period of seventy-two minutes, either during the forenoon or the afternoon, but not directly after a heavy meal. The subject must abstain from food and water during the period of the test. At the beginning of the period, the bladder is emptied. Thirty-six minutes after the test is completed blood is taken from a lobe of the ear and the urea in the whole blood is estimated by means of Bahlmann's [4] micromethod. At the end of the period the bladder is again emptied; this specimen of urine, representing the total amount secreted during the test period, is collected, carefully measured, and used for analysis. The urea in the urine is estimated by the same method as the urea in the blood. The rate of excretion is actually determined for the seventy-two minute period, and calculated for twenty-four hours as a standard period on which to base all the results. McLean had the subject drink from 150 to 200 cc. of water half an hour before the test, but I have usually not found this necessary in my work.

I have chosen Bahlmann's micromethod for the estimation of blood urea, and the test can be carried out daily, if necessary, without harm to the patient since it requires only 0.4 cc. of blood. When there was great edema of the face the blood was taken from the arm vein, lest in taking blood from the lobe of the ear lymph should be mixed with the blood.

The urease, used for the estimation of urea, was prepared from the bean "Nata-mame" (*Canavalia gladiata*) according to Nagasawa's [5] method.[6]

Yanagi [7] modified the apparatus of Bahlmann's micromethod by inserting in the stopper a small funnel whereby the sodium carbonate can be poured into the main tube without danger of the escape of ammonia. When this modified apparatus was used the results were calculated with a slide rule.

INDEX OF PATIENTS WITH NORMAL RENAL FUNCTION

The index of urea excretion in normal persons may vary within wide limits.

4. Bahlmann, R.: Microdetermination of the Content of Urea in Blood by Means of Urease, Nederl. Tijdschr. v. Geneesk, **1**:473-478 (Feb. 7) 1920.

5. Nagasawa, S.: Kyoto-Igaku-Zasshi **17**:54.

6. In 1920 Nagasawa reported that the radicle of the bean "Nata-mame" (*Canavalia gladiata*) contains an enormous quantity of urease, and he prepared a powerful urease from it. I have learned that the cotyledon of the bean also contains considerable urease, and have prepared urease from the cotyledon by the following method After the beans have stood in water at room temperature for twenty-four hours, the skins of the beans are removed, the cotyledons crushed into small pieces, dried in a desiccator, and the residue dried once more. The powder thus obtained is urease.

7. Yanagi, K.: New Colorimetric Method for Determination of Urea with Urease, J. A. M. A. **82**:1169-1171 (April 12) 1924.

For the purpose of studying the limit of normality I have made some observations in a series of patients whose kidneys were found to be intact. The extremes of American authors usually lie between 80 and 200; in my observations of Japanese they are somewhat lower, fluctuating between 60 and 146 (table 1).

TABLE 1.—*Observations on Patients with Normal Renal Function*

Case	Sex*	Age, Years	Diagnosis	Weight, Kg.	Urine in Twenty-Four Hours, Cc.	Urea: Gm. for Each Liter of Blood	Urea: Gm. for Each Liter of Urine	Urea: Gm. for Each Twenty-Four Hours	Index
1	♂	..	Typhoid spine	46.45	1,170	0.21	5.40	6.32	66
2	♀	17	Epilepsy	44.2	1,360	0.52	16.87	22.94	70
3	♂	47	Hemiplegia dextra	48.4	1,900	0.30	10.78	20.48	146
4	♂	44	Carcinoma ventriculi	42.0	500	0.58	33.08	16.54	60
5	♂	27	Pleuritis exsudativa dextra	41.0	1,440	0.43	15.23	21.93	100
6	♂	23	Pleuritis exsudativa sinistra	41.0	600	0.35	18.90	11.34	88
7	♂	44	Amyotrophic lateral sclerosis	44.7	4,600	0.27	2.63	12.10	56
8	♀	25	Pleuritis exsudativa duplex	46.3	1,260	0.28	11.81	14.88	127
9	♀	58	Pachymeningitis cervicodorsalis and cataract	42.5	1,640	0.16	4.50	7.38	139
10	♀	21	Caries of the spine	43.6	1,960	0.37	9.99	19.58	92

* In this and the following tables, ♂ indicates male; ♀, female.

INDEX OF PATIENTS WITH RENAL DISEASE

Albuminuria.—The index was somewhat below normal in two patients whose urine showed only a faint trace of albumin (table 2).

TABLE 2.—*Patients with Albuminuria*

Case	Sex	Age, Years	Diagnosis	Weight, Kg.	Urine in Twenty-Four Hours, Cc.	Urea: Gm. for Each Liter of Blood	Urea: Gm. for Each Liter of Urine	Urea: Gm. for Each Twenty-Four Hours	Index
1	♂	16	Icterus catarrhalis	38.6	860	0.27	6.67	5.75	47
2	♀	31	Amyotrophic lateral sclerosis	40.8	2,100	0.32	4.98	10.46	50

Acute and Chronic Nephritis.—In a series of twenty-four cases of nephritis all the patients were in a serious condition except six (cases 1, 2, 3, 8, 14 and 15, table 3). Albumin was plentiful in the urine in the serious cases, and many blood cells, leukocytes, epithelial cells, hyaline and granular casts were to be found; there was hypertension of varying degree, and edema, which was marked and diffuse in certain cases. The index was low, varying from 1 to 35.

In cases 1, 2, 8, 14 and 15, in which the patients were convalescing from nephritis or were in an improved state with only a faint trace of albumin in the urine and no casts or other abnormalities, the index was

normal or nearly so. The phenolsulphonphthalein test in these cases showed that renal function was almost normal; for example, in case 1 the return was 73 per cent in two hours, and in case 2, 65 per cent. The patient in case 3 was also improving, but diuresis was extreme because of the effect of a diuretic (a decoction of zea 6.0: 100.0), and the kidneys were in an irritable condition.

TABLE 3.—*Patients with Acute and Chronic Nephritis*

Case	Sex	Age, Years	Diagnosis	Test	Weight, Kg.	Urine in Twenty-Four Hours, Cc.	Urea: Gm. for Each Liter of Blood	Urea: Gm. for Each Liter of Urine	Urea: Gm. for Each Twenty-Four Hours	Index
1	♂	26	Acute nephritis	1	54.75	3,600	0.15	2.00	7.20	74
2	♂	22	Chronic nephritis	1	54.6	700	0.26	8.75	6.13	44
3	♀	24	Acute nephritis	1	50.7	2,500	0.12	3.60	9.00	210
4	♀	18	Hemorrhagic nephritis, pleuritis exsudativa sinistra and peritonitis	1	40.0	780	0.34	8.10	6.32	35
5	♂	43	Sclerotic kidney and retinitis albuminurica	1	44.65	2,500	0.40	4.13	10.33	26
6	..	..		2	44.8	2,300	0.76	5.89	13.55	12
7	♂	43	Chronic nephritis	1	40.0	700	0.86	5.10	5.67	5
8	..	..		2	40.0	2,000	0.45	11.25	22.50	83
9	♂	16	Acute nephritis	1	36.2	520	0.55	3.65	1.89	3
10	♂	..	Diabetes mellitus and chronic nephritis	1	43.3	3,100	0.52	2.70	8.37	11
11	..	..		2	44.65	2,480	0.60	1.50	3.72	3
12	♂	..	Diabetes mellitus and chronic nephritis	1	51.9	3,400	0.38	1.30	4.42	6
13	♂	20	Chronic nephritis	1	38.6	2,000	0.35	3.75	7.50	28
14	..	..		2	38.6	1,370	0.24	4.43	6.07	57
15	..	..		3	40.0	900	0.21	4.53	4.08	44
16	♂	55	Chronic nephritis and hemiplegia dextra	1	50.4	2,000	0.37	3.75	7.50	19
17	♂	56	Chronic nephritis	1	66.55	500	1.10	10.80	5.40	2
18	..	..		2	68.40	540	0.96	12.15	6.56	3
19	..	..		3	68.75	380	0.80	16.68	6.34	5
20	..	..		4	69.20	600	1.14	16.43	9.86	4
21	..	..		5	71.20	600	0.89	13.43	8.06	5
22	..	..		6	70.5	400	1.33	17.25	6.90	2
23	♀	25	Sclerotic kidney	1	36.0	1,600	1.01	2.10	3.36	1
24	..	..		2	36.0	1,900	1.12	6.08	11.55	4

Heart Failure.—In the cases of heart failure the index was low in the state of severe decompensation (cases 1 and 2, table 4). When digitalis had increased the diuresis and caused the disappearance of the edema, the index was normal (case 3).

TABLE 4.—*Patients with Heart Failure*

Case	Sex	Age, Years	Diagnosis	Weight, Kg.	Urine in Twenty-Four Hours, Cc.	Urea: Gm. for Each Liter of Blood	Urea: Gm. for Each Liter of Urine	Urea: Gm. for Each Twenty-Four Hours	Index
1	♀	67	Defect of aortic valve with cardiac asthma	41.0	3,500	0.67	2.70	9.45	8
2	♀	36	Defect of mitral valve	34.7	600	0.72	3.62	2.17	2
3	♀	36	Defect of mitral valve	45.0	3,700	0.34	5.40	20.30	100

Mediastinitis.—In a case of mediastinitis in which the circulation was severely disturbed and the edema was marked and diffuse, I found a low index (table 5).

In the experience of Brugi [8] the ureosecretory coefficient during general infection was almost constantly increased. This increase disappeared during convalescence. Aubertin and Rigal [9] showed that a permanent hypertension may coexist with a normal secretion of urea, but I have not observed such cases.

TABLE 5.—*A Patient with Mediastinitis*

					Urea			
Case	Sex	Age, Years	Weight, Kg.	Urine in Twenty-Four Hours, Cc.	Grams for Each Liter of Blood	Grams for Each Liter of Urine	Gm. for Each Twenty-Four Hours	Index
1	♂	44	62.0	2,400	0.88	13.73	33.00	22

SUMMARY

McLean's index is practicable as a test of renal function, although for repeated examinations its value is enhanced by the use of Bahlmann's micromethod for urea determination. The procedure is adaptable to clinical use since it is not necessary to keep the diet constant on account of it. If the index shows a normal value the protein in the diet need not be so rigidly restricted as otherwise.

8. Brugi, A.: Ambard's Coefficient in Infections, Policlinico (sez. med.) **31**:366-372 (July) 1924.

9. Aubertin, C., and Rigal, E.: Ureosecretory Coefficient in Hypertension, Bull et mém. Soc. méd. d. hôp. de Paris **48**:1167-1172 (July 18) 1924.

GASTRIC AND DUODENAL ULCER

FREQUENCY, NUMBER, SIZE, SHAPE, LOCATION, COLOR, SEX AND AGE IN SEVEN THOUSAND SEVEN HUNDRED NECROPSY RECORDS AT BELLEVUE HOSPITAL, NEW YORK *

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The frequency with which statistics of gastric and duodenal ulcer compiled forty or more years ago are quoted in modern systems of medicine and manuals of diseases of the stomach has led us to search the Bellevue Hospital necropsy records from 1904 to 1922 with the purpose of finding out if such figures show any change. A portion of this study is reported here and compared with other published figures, surgical and postmortem. Welch's figures in Pepper's System of Medicine published in 1885, Berthold's statistics in 1882, Leube's tables in Ziemssen's Cyclopedia of 1876, Brinton's figures in his book of 1859 and Lebert's book of 1878 are all examples of statistics covering periods ending more than forty years ago, still doing duty.

While necropsy statistics are open to certain objections [1] in determining the frequency of gastric and duodenal ulcer, they probably afford the best means obtainable.[2] Small scars or ulcers may be impossible of detection or may be overlooked, just as a small ulcer is sometimes difficult or impossible to find at operation.[3] Acute ulcers may leave no scars. A large number of necropsies represents the dead of a charity hospital serving the poor of a large city. Such a group may not represent properly the country, the state, or even the entire city. Medical diagnoses on living subjects, even roentgen-ray diagnoses, must contain a greater percentage of error, while surgical records include only such patients as through the advice of their physicians or from their own initiative seek surgical aid.

The patients of Bellevue Hospital are of all ages. The necropsies are all those permitted on patients who have died in the hospital or

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* From the gastro-enterologic clinic of the University and Bellevue Hospital Medical College.

1. Riegel, Franz: Encyclopedia of Practical Medicine, Disease of the Stomach, 1905, p. 548.

2. Fenwick, Samuel; and Fenwick, W. S.: Ulcer of the Stomach and Duodenum, Philadelphia, P. Blakiston's Son & Co., 1900, p. 78.

3. Sherren, James: Lectures on the Surgery of the Stomach and Duodenum, New York, Paul B. Hoeber, 1922, pp. 18-19.

those performed by the coroner or medical examiner. Bellevue Hospital comprises the following services; gynecology; obstetrics; tuberculosis; psychopathic and nervous diseases; eye, ear, nose and throat; genito-urinary diseases; contagious diseases; baby and children's diseases; erysipelas; alcohol; prison; general medical, and general surgical.

GASTRIC AND DUODENAL ULCER FREQUENCY

In 7,700 necropsy records, 120 cases of gastric ulcer were found, of which thirty-four were healed. In the same 7,700 records, forty-four duodenal ulcers were found, of which nine were healed. In five of these cases, the gastric and duodenal ulcers were found together, making a total of 159 cases in which either gastric or duodenal ulcers were found, or both.

There were eighty-six cases of unhealed gastric ulcers, either single or multiple. There were thirty-five cases of open duodenal ulcer, single or multiple. The eighty-six cases of open gastric ulcer included four

TABLE 1.—*Healed and Unhealed Gastric and Duodenal Ulcers in Seven Thousand Seven Hundred Necropsies*

	Number of Cases	Percentage in 7,700 Necropsies
Healed and unhealed gastric ulcers	120	1.558
Unhealed gastric ulcers	86	1.116
Healed gastric ulcers	34	0.441
Healed and unhealed duodenal ulcers	44	0.571
Unhealed duodenal ulcers	35	0.454
Healed duodenal ulcers	9	0.116
Healed and unhealed gastric and duodenal ulcers	159	2.064
Unhealed gastric and duodenal ulcers	117	1.519
Healed gastric and duodenal ulcers	43	0.558

cases with open duodenal ulcers. These were also counted in the thirty-five cases of open duodenal ulcer, so there were 117 cases of unhealed gastric or duodenal ulcer or both. One patient with open gastric ulcer also had a healed duodenal ulcer.

So in 7,700 necropsy records of the very active service at Bellevue Hospital about 2 per cent had either gastric or duodenal ulcer or had evidence of having had an ulcer. These are somewhat near Berthold's [4] figures of 2.7 per cent, but far from Grunfeld's [5] figures of 20 per cent of necropsies. Bassler [6] compiled 59,450 necropsy records from various sources, the authorities not being given, and states that 4.4 per cent showed open or healed gastric or duodenal ulcers. A series of

4. Berthold, A. H. F.: Statistischer Beitrag zur Kenntnis des chronischen Magengeschwürs, Sections-Protocoll d. Path. Inst. Berlin, 1883, pp. 7-8.

5. Grunfeld, Frederick: Nagle Bemaerkminger om Cikatricer eften Ulcus Ventriculi und Ulcus Duodeni, Hosp. Tid. **60**:765, 1882.

6. Bassler, Anthony: Diseases of the Stomach and Upper Alimentary Tract, Philadelphia, F. A. Davis Company, 1922, p. 562.

8,534 necropsies from the Eppendorf Institute at Hamburg showed about 1.5 per cent of ulcers.[7]

Our figure of 1.5 per cent gastric ulcers is lower than most of the published statistics. Leube [8] in 13,605 necropsies found 653, not quite 5 per cent. Fenwick [2] compiled 47,912 necropsies from various reports, largely Continental, and found 4.2 per cent gastric ulcers. Von Jaksch [9] found 4.8 per cent; Brinton [10] estimated 5 per cent. Welch [11] in a study of 32,052 necropsies, mainly Continental, also estimated 5 per cent. However, in 800 Bellevue Hospital necropsies he found only six ulcers. The following figures all based on necropsy study show the variation of European statistics: Nolte,[12] 1.23 per cent; Stahl,[13] 2.16 per cent; Ziemssen,[14] 4.55 per cent; Griess,[15] 8.3 per cent; Riegel,[1] 10 per cent. The lowest figure found is that of Lebert,[16] one in 200. Lockwood [17] found six in 1,000 necropsies at Bellevue Hospital. He quotes Harlow Brooks' nine in another thousand of Bellevue Hospital necropsies. Lockwood has compiled the figures of 19,315 necropsies in America, including Campbell Howard's [18] figures, and found 238 gastric ulcers, or 1.23 per cent. Among the first thousand necropsies at Johns Hopkins Hospital there were nine gastric ulcers.[19]

The rarity of gastric ulcer in America as compared with Europe has been spoken of by Da Costa,[20] Welch,[11] Howard,[18] Bolton [21] and others.

About 1.12 per cent of our necropsies showed open gastric ulcers. Fenwick's [2] compiled series of 20,317 necropsies showed 1.37 per cent; Hemmeter's [22] figure is 1.4 per cent of 11,888 necropsies, while Leube [8] found 2.33 per cent.

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7. Dietrich, Hans A.: Statistische und ätiologische Bemerkungen zum Ulcus pepticum duodeni, München. med. Wchnschr. **59**:638-640 (March) 1912.
8. Leube, W., cited by H. von Ziemssen in Cyclopedia of the Practice of Medicine, Ulcer of the Stomach, p. 195.
9. Von Jaksch, quoted by Bamberger, H., in Handb. d. spec. Path. u. Therap., Virchow **6**:280, 1855.
10. Brinton, William: Diseases of the Stomach, 1859, p. 133.
11. Welch, W. H.: Pepper's System of Medicine, 1885, p. 480.
12. Nolte, quoted by Hemmeter: Häufigkeit des Magengeschwürs in München, Inaugural Dissertation, 1883, p. 472. Hemmeter, J. C.: Diseases of the Stomach, Philadephia, P. Blakiston's Son & Co., 1897, p. 495.
13. Stahl, quoted by Dreschfeld, Julius: A System of Medicine, Allbutt and Rollston, 1907, **3**:443.
14. Ziemssen, H.: Ueber die Behandlung des Magengeschwürs, Samml. klin. Vortr., 1871, pp. 75-104.
15. Griess, quoted by Hemmeter (Footnote 12, p. 496).
16. Lebert, Hermann: Die Krankheiten des Magens, 1878, p. 180.
17. Lockwood, G. R.: Diseases of the Stomach, Philadelphia, Lea & Febiger, 1913, p. 91.
18. Howard, C. P.: The Incidence of Gastric Ulcer in America, Med. News **85**:673-675 (Oct. 8) 1904.
19. Dreschfeld (Footnote 13).
20. Da Costa, J. M.: Textbook of Medical Diagnosis, 1881, p. 493.
21. Bolton, Charles: Ulcer of the Stomach, 1913, p. 24.
22. Hemmeter (Footnote 12).

Nearly 21 per cent of our ulcers were healed and the proportion of healed to unhealed is very nearly 1:2.5. Leube found the almost equal figures of 278 open ulcers to 265 scars, while Hemmeter's figures were 164 unhealed to 373 healed.

COEXISTENT GASTRIC AND DUODENAL ULCERS

Five patients out of 159 had both gastric and duodenal ulcers. This is just over 3 per cent. Double ulcer is found in over 16 per cent of the Mayos' cases.[23] Perry and Shaw[24] in a series of 120 duodenal ulcers found fifteen cases of concomitant ulcers of the stomach. This is 12.5 per cent, which is not far from our own series of forty-four duodenal ulcers that had coexistent stomach ulcers in 11 per cent. On the other hand, our 120 gastric ulcers had duodenal ulcers in only 4 per cent.

FREQUENCY OF DUODENAL ULCERS

In our series of nearly 8,000 necropsies records of forty-four duodenal ulcers, either open or healed, were found. Nine of these patients had healed ulcers and thirty-five unhealed. Cooley[25] has compiled 38,106 necropsies, 17,652 taken from Perry and Shaw and about 25,000 from German statistics, among which there were 158 duodenal ulcers or scars, 0.41 per cent. Fenwick[2] found 0.26 per cent of 13,055 necropsies.

About 20 per cent of our duodenal ulcers were healed. Brinton[10] in twenty-five ulcers found thirteen healed and twelve open. In Perry and Shaw's[24] cases 11 per cent were healed.

Of 159 healed and unhealed gastric and duodenal ulcers, four patients had both open gastric and open duodenal ulcers. There was one case of open gastric and healed duodenal ulcer. The proportion of gastric to duodenal ulcers was 2.72:1. Only 25 per cent as many patients with gastric ulcers apply to William Mayo for operation as patients with duodenal ulcers; Robson[26] gives 4:3; Einhorn,[27] 4:1, Reed,[28] 12:1.

NUMBER OF GASTRIC ULCERS

Of 120 gastric ulcers eighty-six were single, and of the eighty-six single fifty-six were unhealed. Of our stomach ulcers 71.66 per cent were single. A series of 112 cases from the London Hospital[2] showed

23. Judd, E. S., and Proctor, O. S.: Multiple Gastric Ulcers, M. J. & Rec. **121**:93-95 (Jan. 21) 1925.
24. Perry, E. C., and Shaw, L. E.: On Diseases of the Duodenum, Guy's Hosp. Rep. **50**:171-308, 1893.
25. Cooley, E. B.: Duodenal Ulcer, Illinois M. J. **23**:187-193 (Feb.) 1913.
26. Robson, M. A. W., and Moynihan, B. G. A.: Diseases of the Stomach and Their Surgical Treatment, 1901, p. 93.
27. Einhorn, Max: Diseases of the Stomach, 1900, p. 222.
28. Reed, Boardman: Lectures to General Practitioners on the Diseases of the Stomach and Intestines, 1904, p. 559.

71.43 per cent single. Brinton found 79 per cent single; Leube, 80 per cent, and 80 per cent has been given by other investigators.

The largest number of ulcers counted in any one case was twelve. In five cases the number was given as "numerous" or "multiple." Berthold [4] has described a case of thirty-four gastric ulcers and Lange [29] described a much quoted case in which the ulcers were so numerous as to make it impossible to count them. Affleck,[30] Robertet,[31] Welti,[32] Gaillard [33] and many others have described cases with many ulcers. Bolton [21] mentions two cases of his, one with 431 ulcers and one with 250.

TABLE 2.—*Number of Ulcers in a Single Case, Healed and Unhealed*

		Percentage in 7,700 Necropsies	Percentage in 120 Cases
Single ulcers	86	1.116	71.66
Two ulcers	14	0.181	11.66
Three ulcers	7	0.090	5.83
Four ulcers	2	0.025	1.66
Five ulcers	3	0.038	2.50
Six ulcers	1	0.012	0.83
Eight ulcers	1	0.012	0.83
Twelve ulcers	1	0.012	0.83
Multiple ulcers	5	0.064	4.16
Single ulcers	86	1.116	71.66
Two or more ulcers	34	0.441	28.33

TABLE 3.—*Number of Healed and Unhealed Ulcers in Different Groups in Table 2*

Single Ulcers	Open	Open, per Cent	Healed	Healed, per Cent
86	56	65.11	30	34.89
Number of Ulcers	All Open	One Healed	Two Healed	Three Healed
Two	9	3	2	..
Three	5	..	..	2
Four	2	..	..	..
Five	2	1	..	..

Of 120 gastric ulcers twenty-one were acute, or 17.5 per cent. Figured in proportion to the eighty-six that were open, twenty-one are 24.4 per cent. Fenwick gives 29 per cent of 112 cases as acute. Of our acute ulcers eleven were multiple and ten single, which corresponds with Carless' [34] figure of 50 per cent multiple.

Leaving our acute ulcers out of the foregoing estimate we have ninety-nine chronic ulcers and scars. Of these twenty-three, or nearly 23 per cent, were multiple.

29. Lange: Deutsch. Klinik. **12**:9 (March 3) 1860; ibid. **12**:10 (March 10) 1860.

30. Affleck, J. O.: Tr. Edinburgh Med.-Chir. Soc., Lancet **1**:478, 1901.

31. Robertet: Bull. Soc. anat. de Paris **8**:499-502 (Nov.) 1863.

32. Welti, Emil: Centralbl. f. allg. Pathol. u. path. Anat. **1**:537 (Aug. 5) 1890.

33. Gaillard, M. L.: Bull. et mém. Soc. méd. d. Hôp. de Paris **9**:809 (Nov. 18) 1892.

34. Carless, quoted by Osler, William; and McCrae, Thomas: Modern Medicine **5**:185, 1908.

In each of the remaining cases of multiple ulcers all the ulcers were unhealed.

NUMBER OF DUODENAL ULCERS

Of the twenty-four single ulcers five were healed, leaving nineteen single open duodenal ulcers. This is 43.18 per cent of all duodenal ulcers healed and unhealed and 54.28 per cent of the open duodenal ulcer cases. One of the five patients with single duodenal ulcer scar had an open gastric ulcer. Of the twelve patients having two ulcers, one had both healed; one had one healed. In the case with three ulcers, all three were healed. In one of the cases with five ulcers all five were healed. Of the nineteen patients with single open ulcer, two had open gastric ulcers. Of the ten patients with two open ulcers, one had an open gastric ulcer. The patient with one open ulcer and one scar also had an open gastric ulcer.

In each of the remaining cases of multiple duodenal ulcer all the ulcers were unhealed. One hundred and sixty duodenal ulcers compiled from the literature [24] gave fourteen cases in which two ulcers were present and nine cases in which there were more than two, or

TABLE 4.—*Number of Ulcers in a Single Case, Healed and Unhealed*

		Percentage in 7,700 Necropsies	Percentage in 44 Cases
Single ulcers	24	0.311	54.54
Two ulcers	12	0.155	27.28
Three ulcers	1	0.012	2.27
Four ulcers	1	0.012	2.27
Five ulcers	2	0.025	4.54
Six ulcers	2	0.025	4.54
Twenty-five ulcers	1	0.012	2.27
Multiple ulcers	1	0.012	2.27
Single ulcers	23	0.311	54.54
Two or more ulcers	20	0.259	45.45

14.3 per cent multiple as compared with our 45 per cent. Morat's [35] figures gave 82 per cent single. Sippy [36] stated that more than 20 per cent of duodenal ulcer patients have two or more ulcers. In one of our cases twenty-five ulcers were noted and in another they were described as numerous.

SIZE OF GASTRIC ULCER

Of eighty-six cases of open gastric ulcer five were in infants. These were all acute ulcers. One patient had two ulcers, each 4 mm. in diameter. One patient had three ulcers described as minute. Three patients had one ulcer each, in two instances described as small and in one case the size not being given.

35. Morot, Pierre: Essay sur l'ulcere simple du duodenum, parent imprimeur de la faculté de médecine, 1865.

36. Sippy, B. W.: Nelson Loose-Leaf Medicine **5**:240.

Of the eighty-one cases remaining, there were fifty-three cases of single ulcer. In three of these the size was not given. One case was described as large. In thirty-seven cases one dimension was given and in twelve cases two dimensions were given. Table 5 gives the dimensions in these forty-nine single ulcers.

TABLE 5.—*One or Two Dimensions in Forty-Nine Cases of Single Gastric Ulcer*

Number of Cases	First Dimension, Cm.	Second Dimension, Cm.
2	0.5	...
7	1.0	...
2	1.25	...
4	1.5	...
4	1.75	...
3	2.0	...
5	2.5	...
4	3.0	...
2	4.0	...
3	5.0	...
1	7.0	...
1	0.8	0.4
1	0.5	0.2
1	1.0	1.5
1	1.0	2.0
2	1.5	2.0
1	1.25	2.5
1	2.5	3.0
1	3.0	3.0
1	2.0	3.5
1	3.5	5.0
1	5.0	6.0

There were twelve cases with two ulcers, both open. The size was given in eight of these. Table 6 gives the size of one or both ulcers in the eight cases with two open ulcers.

TABLE 6.—*Dimensions in Eight Cases of Two Open Gastric Ulcers*

Number of Cases	First Ulcer, Cm.	Second Ulcer, Cm.
1	0.5	0.5
1	1.0 by 0.8	Not given
1	1.75	Not given
1	2.5	1.25
1	3.5 by 2.0	1.5
1	4.0 by 1.5	0.4
1	4.0 by 5.0	Not given
1	5.0 by 6.0	2.0

There were five cases with three open ulcers. In one of these the size was not given for any of the ulcers. One was given as from 0.2 to 0.7 cm. for the three ulcers. In one case the size of two of the ulcers was not given while the third was given as 1.5 by 0.5 cm. In the fourth case the size of one ulcer was not given; the other two were measured as 0.4 and 0.75 cm. in diameter, respectively. In the last case the size of two of the ulcers is given as less than 1, while the third ulcer was 2 cm. in diameter.

There were two patients with four open ulcers each. In one of these cases the largest ulcer was 1.5 cm. in diameter; the remainder

were less than 0.5 cm. in diameter. In the other case the ulcers were each less than 0.5 cm. in diameter.

There were three patients with five ulcers each. In one case one of the ulcers was healed. The remaining ulcers were not measured, but in the other two cases all the ulcers were less than 1 cm. in diameter. In one case with six open ulcers all were less than 0.5 cm. in diameter. One patient had eight open ulcers, all less than 1 cm. in diameter.

In the cases described as numerous or multiple one ulcer was 4 by 1 cm. The remainder, such as were given, were all less than 1 cm.

Gastric ulcers may be so small as to be found with great difficulty,[3] or so large as to involve the whole surface of the stomach,[37] or any size between these two extremes. Dreschfeld in Albutt's System of Medicine gives the size as generally less than 2.5 cm. but quotes cases in which the ulcers were 6½ by 3½ inches (16.5 by 8.8 cm.) and 6 by 3 inches (15.2 by 7.6 cm.). Ewald says the size commonly runs from that of a five cent piece to a quarter, which is roughly from 2 to 2.5 cm. Among our forty-nine single ulcers measured the size ranged from less than 0.5 cm. to 5 by 6 cm. The average of the longer measurement given for each ulcer is 2.35. In eight cases with two ulcers, the larger ulcers had the same range as the single ulcers, from 0.5 to 5 by 6 cm. The largest measurement in cases with three ulcers is 2 cm.; in cases with four ulcers, 1.5 cm.; in cases with five ulcers, less than 1 cm. In one case with six ulcers the largest measurement was less than 0.5 cm. Roughly, the ulcers may be said to be smaller as they increase in number in a single case. An exception to this is the ulcer 4 by 1 cm. in a case described as multiple.

SIZE OF DUODENAL ULCERS

Of nineteen open, single duodenal ulcers, the size was given in fourteen. In two cases the ulcers were less than 1 cm. in diameter. Eight had both diameters less than 2 cm. and more than 1 cm. In two the measurements were between 2 and 3 cm. In one the ulcer entirely encircled the intestines. In one the ulcer was described as small.

Of ten cases having two open duodenal ulcers the size was given in seven: In two of these the diameter was 1 cm. in one ulcer and 1 or less in the other; in three cases both ulcers measured between 1 and 2 cm.; in one case one ulcer was 2 cm. in diameter while the other was 2 by 1 cm.; in the seventh case one ulcer was 2 by 0.5 cm., the other 0.4 cm. in diameter.

In one case of four ulcers one ulcer was 2.5 cm. in diameter; the others were all less than 1 cm. One patient with five ulcers had one less than 1 cm. in diameter. In two cases of six ulcers the sizes were

37. Dreschfeld (Footnote 13) p. 450.

not given in either case. One patient had twenty-five ulcers. These were described as running from 2 mm. to 2 cm. In one case with numerous ulcers the size was not given. The duodenal ulcers, except for one that entirely encircled the intestine, ranged from less than 1 cm. to 2 cm. in diameter.

SHAPE OF GASTRIC ULCER

Of eighty-six open gastric ulcers, the shape was given in seventy-eight. Of these fifty were given as round, rounded or circular. This included two cases of three ulcers, all rounded; one case of numerous ulcers, all rounded, and one case of two ulcers, both round. Eighteen cases were described as oval, all single ulcers. Seven cases were irregular. One case had two ulcers, both irregular. Two cases had encircling bands. One ulcer was kidney shaped.

Gastric ulcers are usually round or oval in outline,[2] from which characteristic they are often called round ulcer of the stomach. The authors have been able to find ulcers of the following described: round, oval, irregular, irregularly rounded, triangular, quadrilateral, band shaped, annular, serpiginous, linear, oblong, horseshoe, kidney shaped and starshaped.

SHAPE OF DUODENAL ULCERS

Of thirty-two open duodenal ulcers the shape of twenty-nine was described. Twenty-one were called circular; four were oval, two, irregular, and two band shaped. Duodenal ulcers are almost always oval or rounded. Occasionally they are quadrilateral or annular.

LOCATION OF GASTRIC ULCERS

Table 7 gives the location of the gastric ulcers as far as their location was described.

The relation to the cardia and pylorus is given in 129 ulcers. Fifty-five are at or near the pylorus; ninety-eight are within 8 cm. of the pylorus; eight are at or near the cardia; fifteen are within 8 cm. of the cardia; sixteen are in the midzone between the cardia and the pylorus; nine ulcers are on the anterior surface while twenty-seven are on the posterior surface; forty-one are on the lesser curvature, and nineteen on the greater curvature. The percentage is roughly 76 per cent near the pylorus, 12 per cent near the cardia, and 12 per cent in the midgastric zone.

Of the cases at the Mayo Clinic 90 per cent are in the pyloric end of the stomach. A series published by Charles Mayo in 1921 was: lesser curvature, 534; posterior wall, eighty-five; greater curvature, nine; anterior wall, five, and unrecorded, five. Eusterman's [38] figures

38. Eusterman, G. B.: The Essential Factors in the Diagnosis of Chronic Gastric and Duodenal Ulcers, J. A. M. A. **65**:18 (Oct. 30) 1915.

from the same clinic in 1915 for 264 cases were: lesser curvature, 63 per cent; pylorus, 13 per cent; at or near the pylorus, 33 per cent; posterior wall, 10 per cent, and anterior wall, 2 per cent. In neither of these series are any ulcers mentioned as being near the cardia. Sippy [36] compiled more than 3,000 necropsies, source not given, as follows: lesser curvature, 34 per cent; posterior wall, 30 per cent; pylorus, 12 per cent; anterior wall, 9 per cent; cardia, 6.5 per cent; fundus, 3 per cent; greater curvature, 3.5 per cent, and anterior and posterior wall, 1 per cent. This series gives but a single locating point for each ulcer. A certain number of the 30 per cent on the posterior wall were also probably near the pylorus, yet only those actually in the pylorus are mentioned in this relation. Welch's figures in Pepper's System of Medicine in 1885 and Fenwick's figures in his monograph of 1900 are similar to Sippy's and open to the same criticism.

LOCATION OF DUODENAL ULCERS

The location of forty-seven ulcers was given. Thirty-nine of these were in the first portion of the duodenum. Of this thirty-nine, two extended so as to involve the second portion; the eight remaining were in the second portion. There was no case with one ulcer in the second portion of the duodenum in which there was not one or more ulcers in the first portion.

COLOR AND SEX

Among 7,700 necropsy records searched, 120 gastric ulcers were found, healed and unhealed. Of these 120, 118 were in white persons and two in colored. Eighty-nine patients were male and thirty-one female.

Forty-four records of duodenal ulcers were found. All were in white persons. Of these thirty-four were males and ten females.

The rarity of gastric and duodenal ulcer in negroes has been noted by Wallace Frank and Louis Frank [39] and by Boulware. Apparently, it is rare in the South and rarer still among the colored.

The Fenwicks compiled 2,031 cases of open ulcer and found the proportion three females to two males. They do not say if their records are from postmortem or clinical records. Lebert [16] in 209 clinical cases found three and one-half females to one male. Rokitanski [40] found forty-six female to thirty-three male, while Habershon found 127 women to seventy-four men. Surgical figures give the preponderance very definitely to men. Grouping gastric and duodenal ulcers William J. Mayo [41] finds but little over 25 per cent in women. Necropsy figures

39. Frank, L. W.: Duodenal Ulcer in a Negro, Case Report and Discussion, Kentucky M. J. **20**:74 (Jan.) 1922.

40. Rokitanski, Carl: Med. Jahrb. des. k. k. osterr Staates, 1839, p. 184.

41. Mayo, W. J.: Progress in Handling Chronic Peptic Ulcer, Collected Papers of the Mayo Clinic, 1922, p. 43.

TABLE 7.—*Location of Gastric Ulcers in One Hundred and Twenty Cases Found at Necropsy*

	At Pylorus	Near Pylorus	1 Cm. from Pylorus	2 Cm. from Pylorus	3 Cm. from Pylorus	4 Cm. from Pylorus	5 Cm. from Pylorus	6 Cm. from Pylorus	7 Cm. from Pylorus	8 Cm. from Pylorus	9 Cm. from Pylorus	10 Cm. from Pylorus	11 Cm. from Pylorus	12 Cm. from Pylorus	15 Cm. from Pylorus	19 Cm. from Pylorus	Midway	At Cardia	Near Cardia	1 Cm. from Cardia	2 Cm. from Cardia	3 Cm. from Cardia	4 Cm. from Cardia	5 Cm. from Cardia	6 Cm. from Cardia	7 Cm. from Cardia	8 Cm. from Cardia	Near Lesser Curvature	Near Greater Curvature	No Other Description
Single Ulcers																														
Lesser curvature	3	2	2	..	1	1	3	2	..	1	1	..	..	..	..	1	3	..	..	..	..	..	..	..	..	1	..	..	..	1
Greater curvature	2	..	..	..	..	..	1	..	3	..	..	1	..	1	..	..	4	..	..	..	1	..	..	..	..	..	1	..	..	2
Posterior surface	1	2	..	2	..	..	1	..	..	..	..	..	..	..	1	..	3	..	..	..	..	..	..	..	..	..	..	..	2	..	2
Anterior surface	..	..	..	..	..	1	3	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Pylorus	10	3	2	3	..	1	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Cardia	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Two Ulcer Cases																														
Lesser curvature	..	..	..	..	..	..	..	..	1	5	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
Greater curvature	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2	..	..	..	..	..	..	..	..	..	..	..	..	..	2
Posterior surface	..	..	..	..	..	..	..	..	..	3	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Anterior surface	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Pylorus	3	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Three Ulcer Cases																														
Lesser curvature	..	2	..	1	1	..	2	1	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3	..	..	..
Posterior surface	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..
Cardia	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..
Four Ulcer Cases																														
Pylorus	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3	..	..	..	..	..	..	..	..	..	..	..	..
Cardia	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Five Ulcer Cases																														
Lesser curvature	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Greater curvature	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Posterior surface	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..
Cardia	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Six Ulcer Cases																														
Pylorus	..	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Twelve Ulcer Cases																														
Pylorus	6	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

give about even figures for the most part; Berthold,[4] 128 men to 134 women; Grunfeld,[5] 241 women to 209 men. From our figures we can only say that of the patients dying in Bellevue Hospital for the last twenty years, about three males have gastric ulcer to one female.

The figures for duodenal ulcer show considerable variation in the sex percentage involved. Perry and Shaw [24] found three men to one woman; Mayo (1905), seventy-seven to twenty-three, and Smith [42] in a series of 113 ulcers had ninety-seven cases in males.

Our figures taken from necropsies are almost the same as those of Perry and Shaw similarly taken.

AGE IN GASTRIC ULCER

The age at death of patients in whom gastric and duodenal ulcer is found at necropsy is of little value in determining the age of onset of gastric and duodenal ulcer. Tables 8, 9, 10 and 11, however, are of interest in showing that ulcer may occur at all ages; that from the age of 30 to 50 figures are about the same; that they are doubled from the age of 50 to 60, and that this rate is pretty well maintained from 60 to 69. Obendorfer's [43] table is similar. His group from the age of 20 to 29 is larger proportionately and he has more cases from 70 on. The tables further show that of the kind of persons that go to necropsy at Bellevue Hospital there is an increasing proportion of gastric ulcers found in each ten year group of those dying, up to 70 years at the time of death. Leaving out the cases with scars does not increase the proportion of younger persons in whom ulcer was found at necropsy. That is, there are as many scars in the younger groups as in the older. In the third table the group from the age of 50 to 70 is 46 per cent, while in the first table this group is 52 per cent. Reed [28] says it is a disease of the middle period of life, belonging to the young more than to the old. Our figures fall short of his estimate that three fourths of the patients are between 20 and 60, though well over three fourths of our patients are between 30 and 70. Bassler's "third decade of life" is certainly denied by the numbers of ulcers we have found in advanced life. Many authors make a distinction in the ages of the sexes: Kemp [44] gives 20 to 48 in females, 40 to 50 in males; Abram's edition of Herschell's Textbook of Indigestion gives the average age of females as 27, of males as 36.7; Joslin gives 27 in females, 37 in males; Habershon,[45] from 20 to 50 in males, from 25 to 30 in females. Our table of ages by sexes fits in somewhat with this idea. The youngest

42. Smith, F. J.: Gastric and Duodenal Ulcer, Brit. M. J. **1**:673 (March 19) 1910.

43. Obendorfer: Ueber die Häufigkeit des Ulcus rotundum ventriculi in München, München. med. Wchnschr. **56**:1640, 1909.

44. Kemp, R. C.: Diseases of the Stomach, Intestines and Pancreas, Ed. 2, 1912, p. 252.

45. Habershon, S. H.: Diseases of the Stomach, 1909, p. 378.

woman in the series was between 30 and 40, and there were two in this group. The largest group is from 40 to 50 with five. The 50 to 60 group has nearly as many, while there are as many cases in the 60 to 70 and the 70 to 80 as there are in the 30 to 40. However much it may be a disease of young women it certainly may be present at any age. The men ran older, with the largest group from 60 to 70 .

TABLE 8.—*Age at Death of 117 Patients with Gastric Ulcers, Both Open and Healed, Compared with Age at Death in 7,219 Necropsy Records in Which Age Is Given*

	Number of Cases of Ulcer	Percentage of 117 Cases	Number in Each Group, of 7,219 Cases	Ulcers in Each Group, per Cent
Under 1 year	5	4.273	1,519	0.32
1- 9	0	.....		
10-19	1	0.854	209	0.47
20-29	5	4.273	731	0.68
30-39	17	14.529	1,167	1.45
40-49	19	16.239	1,303	1.45
50-59	34	29.059	1,169	2.9
60-69	27	23.076	760	3.5
70-79	8	6.837	300	2.7
80-89	1	0.854	57	1.7
90-99	0	.....	4	....

TABLE 9.—*Age at Death in Three Hundred and Four Cases Given by Obendorfer*

Age	Number of Cases	Age	Number of Cases
10-19	5	50-59	49
20-29	21	60-69	55
30-39	24	70-79	33
40-49	41	80-89	11

TABLE 10.—*Age at Death of Eighty-Four Patients in Whom Open Gastric Ulcers Were Found at Necropsy*

Age	Number of Cases	Percentage of 70 Cases Over 1 Year
Under 1 year	5	.....
1- 9	0	.....
10-19	1	1.19
20-29	3	3.57
30-39	15	17.85
40-49	13	15.47
50-59	20	23.80
60-69	20	23.80
70-79	7	8.33

TABLE 11.—*Ages at Death of Fifteen Females and Sixty-Four Males with Open Gastric Ulcers*

Age	Females	Males
10-19	0	1
20-29	0	3
30-39	2	13
40-49	5	8
50-59	4	16
60-69	2	18
70-79	2	5

AGE IN DUODENAL ULCERS

Fifty-nine per cent of our patients with duodenal ulcer were between the age of 40 and 70, and 10 per cent were between 70 and 80. In the

TABLE 12.—*Age at Death of Forty-One Patients with Duodenal Ulcers, Open and Healed, Compared with Age at Death of Number of Whole Necropsy Series in Each Age Group*

Age	Number of Cases of Ulcer	Percentage of 41 Cases	Number of Cases in Each Group of 7,219 Cases	Percentage of Ulcers in Each Group
Under 1 year	1	2.43	1,519	0.13
1- 9	1	2.43		
10-19	1	2.43	209	0.47
20-29	6	14.63	731	0.82
30-39	2	4.87	1,167	0.17
40-49	9	21.95	1,303	0.69
50-59	9	21.95	1,169	0.76
60-69	7	17.07	760	0.92
70-79	4	9.75	300	1.33
80-89	1	2.43	57	1.75
90-99	0	.....	4	....

TABLE 13.—*Age at Death of Thirty-Two Patients in Whom Open Duodenal Ulcers Were Found at Necropsy*

Age	Cases	Per Cent
1- 9	1	3.12
10-19	1	3.12
20-29	5	15.62
30-39	1	3.12
40-49	7	21.87
50-59	8	25.00
60-69	5	15.62
70-79	3	9.37
80-89	1	3.12

TABLE 14.—*Age at Death of Nine Females and Twenty-Five Males in Whom Duodenal Ulcer Was Found at Necropsy*

Age	Males	Females
1- 9	1	0
10-19	1	0
20-29	3	2
30-39	1	0
40-49	5	2
50-59	6	2
60-69	5	0
70-79	0	3
80-99	1	0

TABLE 15.—*Ages of Ninety-Five Patients Operated on for Duodenal Ulcer (From Moynihan, 1913)*

Ages	Number of Cases	Per Cent
1-20	0	0
21-30	19	20
31-40	25	26
41-50	33	35
51-60	14	14
61-70	4	4

thirty-two cases with open ulcers exactly 75 per cent were over 40. In the third table, when the sexes are separated the period from 40 to 70 again is the large one while the females are strung along with no particular grouping. Moynihan's table is probably nearer the truth as to the incidence of duodenal ulcer, but our table brings out the fact that there is a considerable group of patients over 40 years without the benefit of surgery. When the number of duodenal ulcers found in each age group is compared with the total number in the necropsy series dying in that group, it will be seen that there is an increasing proportion up to 90 years of age.

SUMMARY

In 7,700 necropsy records at Bellevue Hospital extending from 1904 to 1922, studied as to frequency, number, size, shape, location, color, sex and age in gastric and duodenal ulcer, it was found that gastric and duodenal ulcers taken together are less frequent than most of the published figures. This is owing to the low figures for gastric ulcers since duodenal ulcer frequency runs the same or a little higher than compared figures.

Tabulation of the number of gastric ulcers shows multiple ulcers in about 29 per cent. This compares closely with other figures. About half the duodenal ulcers are multiple; however, this is a higher proportion than we have been able to find in any other statistics.

The average longer measurement for single gastric ulcers is 2.35 cm. The size of the ulcers decreased in each group as the number of ulcers increased, with one exception. The duodenal ulcers ranged from less than 0.5 to 2 cm. in diameter. There was nothing noteworthy when these were grouped according to number of ulcers in a case.

Most of the gastric ulcers were described as round, rounded or circular; nearly 25 per cent. were oval. Almost any shape is possible. Almost all the duodenal ulcers were oval or rounded.

Seventy-six per cent of the gastric ulcers were found near the pylorus; 12 per cent near the cardia, and 12 per cent in the midgastric zone. Of nine cases on the anterior surface three were near the pylorus; one(4 cm. away; three, 5 cm. away, and two were near the greater curvature (table 7). The duodenal ulcers were nearly all in the first portion of the duodenum. In seven cases of multiple ulcer the second portion was involved. Two cases of encircling ulcer extended to the second portion.

Two gastric and no duodenal ulcers were in colored persons. The gastric ulcers were in about three males to one female. The duodenal showed only slightly greater preponderance of males.

Of the 7,700 necropsies 760 were on patients between 60 and 69. Of these 27, or 3.5 per cent, had gastric ulcer. It is found that with the exception of the group aged from 30 to 39 and the 40 to 49 group, which are the same, the percentage of gastric ulcer increases to 70 years, when it falls, as it also does in the 80 to 89 group. The percentage of duodenal ulcers increases for each age group up to 90 years.

EDEMA

I. CORRELATION OF ELASTOMETER FINDINGS, DISAPPEARANCE TIME FOR INTRADERMALLY INJECTED SALT SOLUTION, URINALYSIS AND NITROGEN RETENTION OF THE BLOOD IN EDEMA *

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The rapid disappearance, in children with edema, of the cutaneous elevation produced by intradermal injection of 0.2 cc. of 0.8 per cent salt solution was described by McClure and Aldrich [1] in 1923. They suggested that this test might be of value for detecting disturbed water balance in the tissues, and for following the progress of such disturbance. Later these authors [2] reported this test to be a valuable method for determining immediate prognosis of conditions in children characterized by generalized edema, with albumin, casts and, in some cases, red blood cells in the urine, but unassociated with nitrogen retention in the blood. They also reported the test to be an aid in directing the therapeutic management of these cases. Baker [3] stated that in scarlet fever and diphtheria the disappearance time of intradermally injected salt solution is reduced in proportion to the severity of the intoxication and that the test aids in arriving at a prognosis of these diseases. Harrison [4] reported shortened disappearance time in lobar pneumonia in children with a slow return to normal after crisis and with no constant relationship between the height of the fever and the length of the disappearance time. The normal disappearance time is considered as being longer than one hour for children, and somewhat longer still for adults. In this paper we deal only with adults.

As the edema described by McClure and Aldrich was determined by tactile estimation (a method of questionable delicacy) it seemed advisable to correlate the disappearance time of the intradermally injected salt solution with findings obtained by the use of Schade's [5] elastometer.

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* From the Otho S. A. Sprague Memorial Institute and the Pathological Laboratory of the Cook County Hospital.

1. McClure, W. B., and Aldrich, C. A.: Time Required for Disappearance of Intradermally Injected Salt Solution, J. A. M. A. **81**:293-294 (July 28) 1923.

2. Aldrich, C. A., and McClure, W. B.: Intradermal Salt Solution Test; Its Prognostic Value in "Nephritis" with Generalized Edema, J. A. M. A. **82**:1425-1428 (May 3) 1924.

3. Baker, W. J.: Intradermal Salt Solution Test in Scarlet Fever and Diphtheria Patients, J. A. M. A. **83**:1566-1567 (Nov. 15) 1924.

4. Harrison, Jeanette: Intradermal Salt Solution Test in Lobar Pneumonia in Children, J. A. M. A. **84**:1258-1259 (April 25) 1925.

5. Schade, H.: Ztschr. f. exper. Path. u. Therap. **11**:369, 1912.

Schwartz [6] and others [7] found that by means of this instrument one could detect degrees of edema not appreciable by the palpating finger, and at the same time secure a graphic quantitative record of the condition. Our results confirm this statement. It is impossible to express in mathematical terms the degree of edema present, as determined with the elastometer, because the height of the curve depends entirely on the closeness of contact that the disk bearing the weight makes with the surface of the skin. However, the character of the curve and the deficiency of return to the base line gives an objective index of the approximate amount of edema, not accurately obtainable with the palpating finger. It must be remembered, in this connection, that the elastometer gives no information as to the generalization of the condition of edema. It is an index only of the edema in the exact area to which the tactile disk is applied, just as is the case with the palpating finger. But the elastometer furnishes a means for producing an objective

TABLE 1.—*Elastometer Findings, Disappearance Time for Intradermally Injected Salt Solution, and Body Temperature in Typhoid Fever Without Palpable Edema* *

Case	Date	Elastometer Findings on Dorsum of Wrist	Widal Reaction	Body Temperature, Fahrenheit	Disappearance Time for Intradermally Injected Salt Solution
1 (A.B.)	7/30	0	+	100.2	65 minutes
2 (S.M.)	8/11	0	+	102.0	1 hour, 15 minutes
3 (J.A.)	8/12	0	+	100.2	1 hour, 15 minutes
4 (K.L.)†	9/ 2	0	Negative	99	35 minutes
5 (S.T.)	9/25	0	+	100	1 hour, 25 minutes
6 (L.C.)	9/26	0	+	100.8	1 hour, 15 minutes
7 (E.N.)	9/26	0	+	104.8	1 hour, 25 minutes

* Urinalysis of the cases showed no albumin, blood or casts.
† Typhoidal thrombophlebitis was suspected.

record, thereby eliminating error due to differences in the ability of individuals to discriminate between different degrees of pitting and between slight pitting and normal elasticity of the skin, and it records degrees of edema too slight to be detected by palpation.

In this report, all elastometer curves and intradermal salt solution tests are made on the dorsum of the wrist unless otherwise stated. The technic for using the elastometer is described by Schwartz.[6] Our purpose in this work is to determine what relationship, if any, exists between the disappearance time of intradermally injected salt solution, elastometer findings, body temperature, nitrogen retention in the blood and pathologic urinary findings.

Table 1 gives the results obtained from seven cases of typhoid fever. Six of these show a normal length of time for the disappearance of

6. Schwartz, A. B.: Edema, Arch. Int. Med. **17**:396-404 (March) 1916.
7. Maver, Mary E., and Schwartz, A. B.: Edema in Pneumonia, Arch. Int. Med. **17**:459-464 (April) 1916. Schade (Footnote 5).

intradermally injected salt solution although the body temperature of the patients ranges from 100.2 to 104.8. Urinalysis at no time showed albumin, casts or blood. The elastometer curves, as seen in figure 1, show no edema, except a very slight degree in case 4 (K. L.). Here the disappearance time was also reduced but the patient was suffering from thrombophlebitis of the leg as well as from a condition suspected as being typhoid. No pitting could be detected at the ankles with the palpating finger. These results indicate that increase in body temperature up to 104.8 does not of itself shorten the disappearance time for intradermally injected salt solution; also that in uncomplicated typhoid fever there may be no tendency toward edema as determined by the elastometer.[8]

Table 2 shows the results obtained from a group of seven women in the pathologic obstetric ward. All were suffering from acute toxemia of

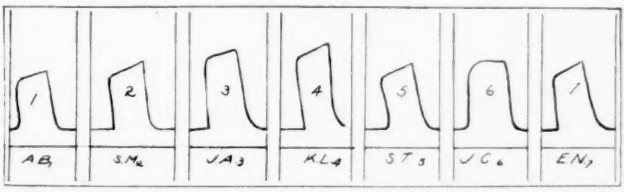

Fig. 1.—Absence of edema in uncomplicated typhoid, when there was no shortening of disappearance time of intradermally injected salt solution. An elastometer curve obtained from a nonedematous person with normal elasticity of the skin shows a tendency to plateau formation of the horizontal phase with prompt return to the base line of the down stroke. All curves in this figure, except curve 4, have the characteristics of curves obtained from normal individuals. Curves 1, 2, 3, 4, 5, 6 and 7 were obtained from patients with typhoid fever (table 1); the disappearance time for intradermal injected salt solution was slightly shortened in case 4 (K. L., curve 4); curve 4 shows slight edema; the typhoid here is complicated by thrombophlebitis of the leg.

pregnancy, with or without eclampsia. The disappearance time of the intradermally injected salt solution was markedly short in all cases except case 3 (A. B), in which shortening, though present, is less pronounced. This effect of the toxemias of pregnancy on the disappearance time has also been shown by Lash[9] with patients from the same ward. Slight palpable edema at the ankles could be detected in cases 1 (R. B.), 3 (A. B.) and 4 (V. L), a condition probably due in part to pressure by the gravid uterus on the pelvic vessels. In these three cases and also in case 5 (L. W), edema could be detected at the dorsum of the wrist by means of the elastometer (fig. 2), but could not be detected by palpation.

8. A series of cases of typhoid fever was also tested by S. A. Leader, who likewise found no decrease in the disappearance time.

9. Lash, A. F.: Surg. Gynec. Obst., to be published.

The urine of this group, except case 2 (O. N.), is characterized by a large content of albumin and in some cases the presence of casts. Blood chemical findings in the four cases analyzed show some nitrogen retention, but the amount of nitrogen retention bears no relationship to reduction in disappearance time of the intradermally injected salt solution. The elastometer curves may return to normal several days or weeks before the return to normal of the disappearance time for intradermally injected salt solution. The findings in this group suggest that when the disappearance time is short and no palpable edema is demonstrable, slight edema may in some cases be detected with the elastometer. But in other cases the shortened disappearance time is the only index obtainable of a disturbed water balance in the tissues.

TABLE 2.—*Data on Cases of Toxemia of Pregnancy*

		Urinalysis		Blood Chemistry							
Case	Date, 1925	Albumin	Casts	Total Nitrogen	Non-protein Nitrogen	Urea Nitrogen	Creatinine	Uric Acid	Palpable Edema Region Most Marked	Elastometer Findings on Dorsum of Wrist	Disappearance Time for Intradermally Injected Salt Solution, Minutes
1 (R. B.)	3/29	++++	+	2.660	.....	18.60	1.5	3.9	Ankles	Slight edema	10-20
	3/31	++++	+	2.758	42.30	.....	....	...	Ankles	None	20
	4/ 5	+++	+	.....	.....	.....	....	...	Ankles	None	30
	5/15	+	0	.....	.....	.....	....	...	None	None	45
2 (O. N.)	3/28	0	0	2.800	.....	11.64	1.43	1.76	None	None	25
	4/24	0	0	.....	.....	.....	....	...	None	None	40
3 (A. B.)	3/24	++++	++	.....	39	19.00	1.47	1.6	Ankles	Slight edema	50
	4/ 2	0	0	2.390	30	11.2	....	...	None	None	50
	4/ 6	0	0	.....	.....	.....	....	...	None	None	50
4 (V. L.)	4/21	++++	+	.....	.....	.....	....	...	Ankles	Slight edema	10
	5/ 1	+	0	.....	.....	.....	....	...	None	None	30
5 (L. W.)	5/12	++	+	.....	.....	.....	....	...	None	Slight edema	14
6 (E. G.)	6/ 6	++	0	.....	.....	.....	....	...	None	None	30
7 (J. S.)	5/ 1	++++	0	.....	.....	.....	....	...	None	None	40

Widal [10] has stated that 6 Kg. of water may be retained in the adult before pitting can be detected. These cases with shortened disappearance time and no manifestations of edema may be cases in which the amount of water retention is not sufficient to be detected even with the elastometer, but in which a disturbed water balance is an active process, as indicated by the short disappearance time. This disturbed water balance in some instances may lead to edema demonstrable with the elastometer; in others, the process may be interrupted, resulting in a lengthening of the disappearance time and return to a normal water

10. Widal, F., and Lemierre, A.: Ergebn. der inn. Med. u. Kinderh. **4**:523, 1909.

balance of the tissues before a retention sufficient to be detected with the elastometer has occurred. Or again, shortened disappearance time without edema may mean that the tissues have an increased affinity for water, but that for some reason water is not available to satisfy this increased affinity.

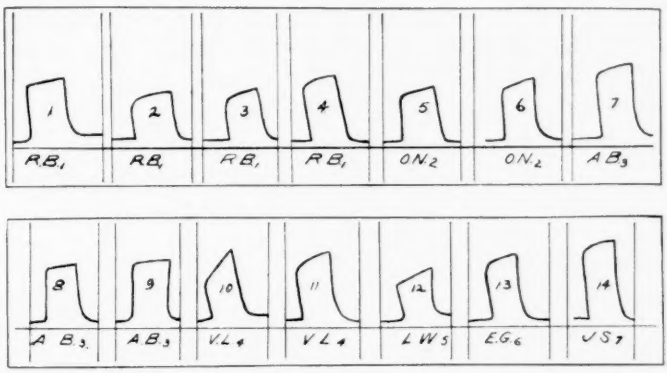

Fig. 2.—Fourteen elastometer curves from seven cases of toxemia of pregnancy (table 2); no edema could be detected with the palpating finger, but the elastometer shows edema in curves 1, 10 and 12 by the deficient return of the down stroke to the base line; a loss of elasticity is indicated in curves 10 and 12 by the sharp inclination of the horizontal line; the time for the salt solution test is markedly reduced in all these cases except case 3 (A. B.); curves 7, 8 and 9 were obtained from this patient.

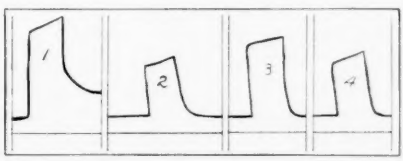

Fig. 3.—Curves obtained during critical period and period of recovery of patient 1 (C. N.) with acute nephritis. The elastometer ceases to give evidence of edema three weeks before the disappearance time is normal. Curve 1, March 22, shows marked edema, with disappearance time fifteen minutes; curve 2, March 30, no edema, with disappearance time from twenty to twenty-eight minutes; curve 3, April 29, no edema, with disappearance time from forty-five to fifty minutes, and curve 4, May 15, no edema, with disappearance time fifty minutes.

Table 3 shows the results obtained from fifteen cases of nephritis, one case of edema due to cardiac decompensation, one case of nutritional edema, one case of localized edema supposedly due to lymphatic obstruction, one case of bichloride of mercury poisoning, and three cases of hypertension. Cases 1 to 9, inclusive, are characterized by a reduced disappearance time, albumin in the urine in all except case 7 (T. D.)

and, in some cases, blood and casts. Nitrogen retention in the blood is marked in some cases, slight in others. The cases of acute nephritis studied most extensively need separate discussion because of their different clinical courses and terminations.

During the time that the condition was grave case 1 (C. N.) had a disappearance time of fifteen minutes. Edema was marked and generalized. As the edema subsided the disappearance time lengthened a little but remained markedly reduced several weeks after edema could no longer be detected with the elastometer (fig. 3). The presence of

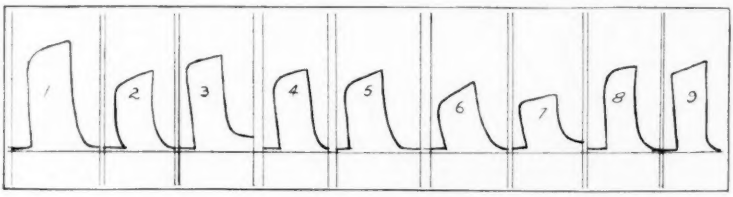

Fig. 4.—Elastometer curves obtained from patient 2 (J. C.) with acute nephritis with no marked palpable edema over dorsum of wrist. The disappearance time at the dorsum of the wrist was never less than twenty minutes; curves 1, 2, 4, 5, 6, 8 and 9 show no edema. At the time these curves were made the disappearance time was from thirty-one to fifty-five minutes; curve 3 shows slight edema, with disappearance time twenty minutes.

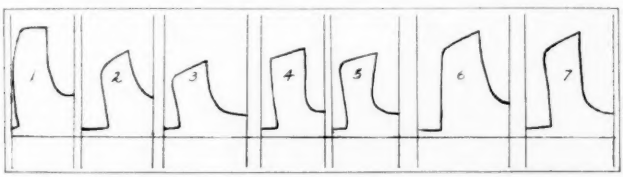

Fig. 5.—Curves obtained from patient 3 (J. S.) with acute nephritis and very marked palpable edema. The patient did not recover; the disappearance time persistently remained less than ten minutes, except the day that curve 4 was obtained, July 30, 1925, when the disappearance time was thirty minutes.

albumin and casts in the urine and nitrogen retention in the blood bear no relationship to the length of the disappearance time or the character of the elastometer curve. After the disappearance time increased to thirty minutes no edema could be detected with the elastometer. This same condition holds in case 2 (J. C.) (fig. 4). Both these patients made a complete recovery.

In case 3 (J. S.), acute nephritis with marked edema and fatal termination, the disappearance time during the entire course (from June 4 to July 19), except one test, was reduced to eight and ten minutes. The elastometer showed marked edema (fig. 5) which never

subsided. Urinalysis shows albumin, blood and casts. There also was nitrogen retention in the blood.

Figure 6 shows elastometer curves obtained from patient 5 (G. T.) with acute mercurial poisoning. Curve 1 was obtained about two and one-half hours after the sublimate had been swallowed. During this time the patient had been brought to the hospital and the usual antidotes were effectively administered. The disappearance time was normal (sixty-five minutes). No edema could be detected with the elastometer. Urinalysis showed no albumin, blood or casts. Two days later the disappearance time was reduced to thirty minutes, and remained so

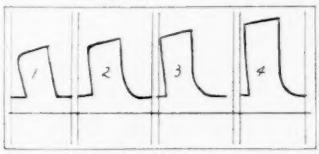

Fig. 6.—Curves in case 7 (G. T.) of acute mercuric chloride poisoning. Curve 1 shows no edema, with disappearance time sixty-five minutes; curves 2, 3 and 4 show no edema, with disappearance time thirty minutes. The lessened disappearance time is the only indication of disturbed water balance in the tissues.

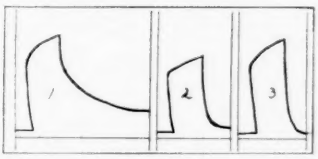

Fig. 7.—Curves of case 7 (T. D.) of generalized palpable edema due to cardiac decompensation; in this case the disappearance time returned to normal, as soon as the demonstrable edema disappeared. Curve 1, July 27, shows marked edema, with disappearance time from two to three minutes; curve 2, August 1, slight edema, with disappearance time twenty-five minutes, and curve 3, August 3, no edema, with disappearance time sixty minutes.

during the following week, at the end of which time the patient was discharged from the hospital. No edema could be detected with the elastometer during this period of shortened disappearance time. This again is a case in which the reduced disappearance time is the only obtainable evidence of disturbed water balance in the tissues.

In case 7 (T. D.), generalized edema due to cardiac decompensation, the disappearance time was from two to three minutes, during the period of most marked edema, but in less than a week of rest in bed and medication the edema had completely subsided. In this case the disappearance time became normal as soon as the edema could no longer be demonstrated (fig. 7) by the elastometer. This is a striking contrast

to the picture in acute nephritis in which the disappearance time may remain shortened weeks after the elastometer curve is normal.

The effect of localized edema on the character of the elastometer curve is shown in figure 8. The disappearance time over the area of localized edema is fifteen minutes. These curves were obtained from the ankles of a man, patient 11 (M. C. P.), with marked edema of the right leg, believed to be the result of lymphatic obstruction, no. 1 being from the normal leg, disappearance time one hour and twenty-five minutes, and no. 2 from the edematous leg.

Studies made on patient 12 (H.) demonstrate clearly that the reduction in disappearance time precedes the ability to detect edema with

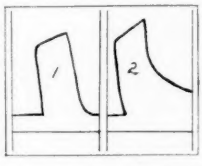

Fig. 8.—Influence of localized edema on character of elastometer curve in case 11 (M. C. P.). Curve 1 was obtained from normal left leg, with disappearance time one hour and twenty-five minutes; curve 2, obtained from right leg, shows edema due to localized lymphatic obstruction, with disappearance time of fifteen minutes.

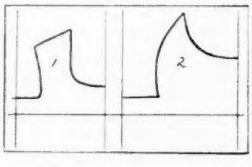

Fig. 9.—Nutritional edema in case 12; a decreased disappearance time precedes the ability to demonstrate edema with the elastometer. The disappearance time on the dorsum of the wrist gradually lessened from fifty-five minutes, June 30, 1925, to thirty minutes, July 10, 1925; no edema was demonstrable at the dorsum of the wrist by the elastometer until July 10, 1925 (curve 1); curve 2 shows edema at the leg on that day, when the disappearance time was four minutes.

the elastometer (fig. 9). This subject, a man, aged 36, voluntarily undertook for another study a total fasting experiment extending over thirty-three days and resulting in marked edema during the week following the termination of the experiment. Before the experiment was begun, May 27, 1925, the disappearance time at the dorsum of the wrist was one hour. At the end of the experiment, June 30, 1925, the disappearance time at the wrist was fifty-five minutes; at the leg, forty-five minutes; there was no pitting of the arm and slight pitting of the legs. July 2, the disappearance time on the dorsum of the wrist was fifty-five minutes; of the leg, thirty minutes. July 7, it was forty minutes at the

wrist and eight minutes on the leg. At this time there was marked palpable edema of the leg, but none of the arm. July 10, the disappearance time at the wrist was thirty minutes, on the leg four minutes. On this day edema of the arm could be detected by the elastometer for the first time. These findings at the wrist unquestionably prove that a shortening of the disappearance time precedes the ability to detect edema with the elastometer.

Figure 10 illustrates elastometer curves obtained from a group of eight cases of chronic nephritis without edema, with and without hypertension, and one case of arteriosclerotic hypertension, case 21 (M. A.). The disappearance time for the intradermally injected salt solution is normal in this group of cases; urinalyses show albumin in all except case 21 (M. A.). In some cases nitrogen retention in the blood also is marked (case 16, D. M. C., table 3). The elastometer curves show no evidence of edema. Evidently, then, albuminuria and nitrogen retention may occur without the existence in the skin of the

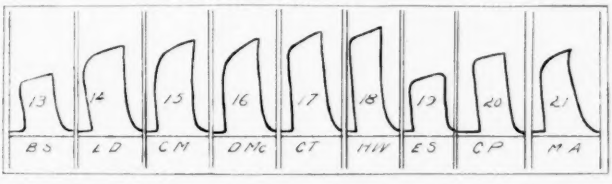

Fig. 10.—Curves obtained from eight patients with chronic nephritis and one with hypertension; no edema could be detected with the elastometer; the disappearance time was normal; nitrogen retention of the blood was marked in some cases; albumin appeared in the urine of all (table 3), excepting case 21, M. A.

changes usually associated with edema, that is, shortened disappearance time and loss of elasticity.

SUMMARY

1. In uncomplicated typhoid fever, no edema was demonstrable with the elastometer. The disappearance time for intradermally injected salt solution was normal, although the body temperatures in the cases studied ranged from 99 to 104.8.

2. In acute toxemias of pregnancy the disappearance time was reduced to approximately ten minutes before edema could be detected with the elastometer of Schade.

3. In acute nephritis the disappearance time fell to thirty minutes or less before edema could be detected with the elastometer.

4. In a series of cases of chronic nephritis with albuminuria and nitrogen retention, no edema could be demonstrated with the elastometer and the disappearance time for intradermally injected salt solution was normal.

TABLE 3.—*Data in Cases of Nephritis and Related Conditions*

Case	Date, 1925	Palpable Edema Region Most Marked	Edema on Dorsum of Wrist as Determined by Elastometer	Disappearance Time for Intradermal Salt Solution Test at the Wrist, Minutes	Urinalysis			Blood Chemistry					Clinical Diagnosis	Remarks
					Albumin	Blood	Casts	Non-protein Nitrogen	Urea Nitrogen	Urea	Uric Acid	Creatinine		
1 (C.N.)...	3/22	Generalized	+++	15	++	0	++	39	....	18	....	1.5	Acute nephritis	
(C.N.)...	3/30	Lower extremities.....	0	25-28	++	0	+	....	....	49.9	2.9	1.7	.....	Condition improving
(C.N.)...	4/21	Ankles	0	45-50	++++	0	++	....	24	51.9	1.5	1.8	.....	Marked improvement
(C.N.)...	5/15	Slight at ankles.....	0	50	0	0	0	....	....	....	....	....	.....	Discharged from hospital
2 (J.C.)...	3/23	None	0	55	+++	++	+	....	....	....	....	....	Acute nephritis	
(J.C.)...	4/20	Over lumbar vertebrae	0	30	+++	++	+	....	....	....	....	....		
(J.C.)...	5/ 8	Over lumbar vertebrae	+	20-25	+++	++	+	....	....	....	....	....		
(J.C.)...	5/18	Over lumbar vertebrae	0	40	++++	++	0	....	....	....	....	....		
(J.C.)...	6/18	Ankles	0	50	++++	+++	+	....	....	....	....	....		
(J.C.)...	7/13	Ankles	0	50	++++	0	+	....	....	....	....	....	.....	Sent home
(J.C.)...	8/22	Face and legs.....	+	30	+++	0	+	....	....	....	....	....	.....	Returned to hospital
(J.C.)...	9/ 2	Ankles	0	55	++++	+++	0	28	10.2	21.9	1.7	1.4		
(J.C.)...	9/13	Ankles	0	55	++++	+++	0	38	....	38.9	2.5	1.5	.....	Condition improved
3 (J.S.)....	6/ 4	Markedly generalized..	+++	5-7	+++	++++	++	68.9	....	17.2	3.85	3.75	Acute exacerbation of chronic nephritis	
(J.S.)....	6/19	Markedly generalized..	+++	10	+++	+++	++	....	....	....	....	....		
(J.S.)....	6/20	Generalized, but not so marked	++	10	+++	+++	++	....	....	....	....	....		
(J.S.)....	7/13	Lower extremities.....	+	30	+++	+++	++	73	....	47.1	3.53	2.2	.....	Marked disappearance of edema
(J.S.)....	7/14	Generalized	+++	5-8	+++	+++	++	....	....	....	....	....	.....	Condition much worse
(J.S.)....	7/19	Markedly generalized..	+++	6-8	++++	+++	++	....	....	....	....	....	.....	Died
4 (J.C.)...	6/ 8	Generalized	+++	10	+++	+++	++	....	....	....	....	....	Parenchymatous nephritis	
5 (G.T.)...	8/ 1	None	0	65	0	0	0	....	....	....	....	....	Mercuric chloride poisoning	
(G.T.)...	8/ 3	None	0	30	+	+	+	....	....	....	....	....		
(G.T.)...	8/ 7	None	0	30	0	0	0	....	....	....	....	....		
(G.T.)...	8/ 8	None	0	30	0	0	0	....	....	....	....	....	.....	Sent to psychopathic hospital

Case	Date, 1925	Palpable Edema Region Most Marked	Edema on Dorsum of Wrist as Determined by Elastometer	Disappearance Time for Intradermal Salt Solution Test at the Wrist, Minutes	Urinalysis			Blood Chemistry					Clinical Diagnosis	Remarks
					Albumin	Blood	Casts	Non-protein Nitrogen	Urea Nitrogen	Urea	Uric Acid	Creatinine		
6 (M.B.)...	6/20	Markedly generalized..	++	8	+++	0	++	....	....	....	....	....	Acute exacerbation of chronic nephritis	
7 (T.De)...	7/27	Markedly generalized..	+++	2-3	0	0	0	....	....	....	....	....	Cardiac decompensation	
(T.De)...	8/ 1	Lower extremities.....	+	25	0	0	0	....	....	....	....	....	.....	Sent home
(T.De)...	8/ 3	Lower extremities.....	0	60	0	0	0	....	....	....	....	....	.....	
8 (S.F.)...	9/23	Generalized	+	14	+	0	0	36.8	....	33.9	....	1.5	Chronic parenchymatous nephritis	Cardiac complications; systolic blood pressure, 220, diastolic, 180
9 (L.S.)...	9/25	Lower extremities.....	+	25	++	0	++	36.2	....	33.95	....	1.5	Acute exacerbating chronic nephritis	
10 (E.B.)...	9/15	Ankles	+	45	+	0	0	....	13.07	....	1.90	1.44	Hypertension; cardiac hypertrophy	Systolic blood pressure 230, diastolic, 100
11 (M.C.P.)	6/ 3	Right lower leg only..	++	15*	0	0	0	....	....	....	....	....	Localized obstruction of lymphatics	Absorption time of right lower leg, 5 minutes
12 (H.).....	7/ 2	Lower extremities.....	0	55	0	0	0	....	....	....	....	....	Nutritional edema	Cardiac complication
(H.).....	7/10	Generalized	+	30	0	0	0	35	15.4	32.9	3.8	1.5		
13 (B.S.)...	8/17	Slight at ankles.....	0	75	++	0	+	....	....	71.9	3.2	3.0	Chronic nephritis	
14 (L.D.)...	8/20	None	0	75	++	0	0	27	....	9.3	1.28	1.2	Chronic nephritis; arterial sclerosis	
(L.D.)...	8/28	None	0	75	++	0	0	....	20.5	....	2.6	1.5		
15 (C.M.)...	5/27	None	0	60	+++	0	0	....	....	....	....	....	Chronic nephritis	
16 (D.M.C.)	8/19	None	0	70	+	0	0	....	....	88	3.1	3.7	Chronic nephritis	
(D.M.C.)	9/ 6	None	0	75	+	0	0	....	....	51	3.1	1.7		
17 (C.T.)...	8/21	None	0	60	++	0	+	....	....	21	2.4	1.6	Chronic nephritis	
18 (H.W.)..	9/20	Ankles	0	85	+	0	+	....	....	23	3.3	1.6	Chronic nephritis	
19 (E.S.)...	9/21	None	0	75	++	0	+	....	....	34.5	....	....	Chronic nephritis	Systolic blood pressure, 195, diastolic, 80
20 (C.P.)...	8/18	None	0	85	+	0	0	....	28.02	....	2.3	2	Chronic nephritis	Systolic blood pressure, 210, diastolic, 165
21 (M.A.)..	9/16	None	0	75	0	0	0	....	....	....	....	....	Hypertension; arterial sclerosis	Systolic blood pressure, 250, diastolic, 100
22 (M.O.)..	9/19	Ankles	+	30	0	0	0	37	16.8	....	1.85	1.5	Hypertension; chronic myocarditis; arteriosclerosis	Systolic blood pressure, 250, diastolic, 100

* In this case the disappearance test was made over edematous part of right leg. The disappearance time of the corresponding area on the left leg was one hour and thirty minutes.

5. Conditions causing the appearance of albumin and casts in the urine and nitrogen retention in the blood are not necessarily causal factors in shortening the disappearance time for intradermally injected salt solution.

6. A decrease in disappearance time precedes the ability to detect edema with the elastometer.

7. In acute nephritis with disappearing edema the elastometer curve becomes normal several days or weeks before the disappearance time becomes normal. In edema due to cardiac decompensation the disappearance time may become normal as soon as the edema has subsided, as determined by the elastometer.

8. That both the elastometer curve and the disappearance time for intradermally injected salt solution are markedly influenced by conditions in localized areas [11] must be taken into consideration in using these tests as an index to generalized conditions. For comparative work the two tests must be made over the same area.

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11. Cohen, M. B.: Intracutaneous Salt Solution Test: Preliminary Report of Simple Method for Determining Efficiency of Circulation in Extremities, J. A. M. A. **84**:1561 (May 23) 1925.

STENOSIS OF THE ISTHMUS (COARCTATION) OF THE AORTA AND ITS DIAGNOSIS DURING LIFE

REPORT OF FOUR CASES *

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Congenital cardiovascular lesions are, as a rule, multiple; they present confusing physical signs and are apt to produce a number of different diagnoses. Coarctation (congenital stenosis) of the aorta produces outspoken clinical signs, which, when present in characteristic form, may be recognized at a glance.

It is a curious fact, however, that the diagnosis is rarely made during life. Case 1 of this series was the only case on record in the Johns Hopkins Hospital case histories during the first thirty-four years of its existence (1889-1923). Since that time three additional cases have been found in the wards and outpatient departments of this hospital, and we are inclined to believe that other patients with this condition may have gone through our hands unrecognized because of the lack of familiarity with the clinical picture, or possibly because of the lack of outspoken physical signs. This impression is strengthened by postmortem reports, which show that coarctation of the aorta is not uncommon; for example, Fawcett [1] found eighteen cases of coarctation in a routine postmortem examination of 22,316 persons, or almost one per thousand. The diameter of the aorta at the site of the stenosis varied from one-half inch (1.27 cm.) to a narrow opening that barely admitted a fine probe, while in one case there was total obliteration of the aorta. No case in Fawcett's series had been recognized during life.

It would be of no especial interest to attempt to summarize the reported cases of coarctation since this has been done particularly well from time to time. For this reason Abbott [2] believes that the twelve cases analyzed by her in 1915 probably represent the total number of cases recognized during life and postmortem more nearly than is the case with reports of other congenital cardiovascular lesions. A recent bibliography has not been found in the literature, and we have tried to compile one that includes most of the reported cases.

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* From the medical clinic, Johns Hopkins University Medical Department.

1. Fawcett, John: Coarctation of the Aorta, as Illustrated by Cases from the Postmortem Records of Guy's Hospital from 1826-1902, Guy's Hosp. Rep. **59**, Series 111; **44**:1, 1905.

2. Abbott, M.: Osler and McCrae's Modern Medicine, Philadelphia, Lea and Febiger, 1915.

The cases included in this paper are reported to call attention to a condition that is unfamiliar to most physicians, to place the cases on record and to emphasize a few details of diagnosis.

Coarctation of the aorta must be distinguished from other anomalies of the aorta, such as a generalized hypoplasia and the various other defects of the aortic arch. By true coarctation is understood a comparatively sharp constriction or more diffuse stenosis, sometimes a total obliteration, of that portion of the thoracic aorta lying between the left common carotid artery and the entrance of the ductus botalli.

It should be remembered that this portion of the aorta, which is known as the isthmus, performs a minimal function during embryonic life, since the prenatal patency of the ductus botalli allows a considerable quantity of blood to pass directly into the aorta below the isthmus, while the vessels proximal to the isthmus supply all the upper part of the body. For this reason it is not remarkable that this portion of the aorta should be the site of persistent narrowness or even obliteration, when abnormalities of development occur. The so-called infantile type of coarctation, usually a rather diffuse narrowness of the isthmus—and usually fatal—is thought to be due to such an error in development. The adult variety, however, to which all of our four cases probably belong, consists of a rather sharp constriction of the aorta at or near the entrance of the ductus. It is thought to arise postnatally and is most reasonably explained by the skodaic theory. This theory explains the constriction of the aorta by assuming an extension of the tissue of the ductus into the adjacent wall of the aorta; it is thought that this tissue contracts after birth along with the tissue of the ductus botalli. In favor of the theory is the fact that the adult type of coarctation has not been noted before birth; against it is the fact that the isthmus begins normally to function fully at a time when the ductus is being obliterated: the obliteration of the ductus is aided by a marked drop in pressure behind it when the pulmonary circulation begins to function, while the isthmus is strained by a marked increase in blood volume passing through it, and a constriction developing in the face of such increased function is a theory difficult to grasp. We have, however, no better explanation to offer.

Priority in recognition of coarctation is given by Abbott [2] to Paris [3] (1789). Meckel's [4] case was apparently one of diffuse hypoplasia of the aorta, but Morgagni [5] may have described in 1760 a case of true coarctation from a postmortem on a monk. Morgagni said: "A short distance from the heart the aorta was contracted to an astonishing

3. Paris: Case of Considerable Contraction of the Aorta, translated into English by R. Gosling, London, Chir. d. Desault **11**:107, 1789.

4. Meckel, Johann: Nachr. d. Acad. d. Wissensch., Berlin, 1755.

5. Morgagni, G. B.: De Sedibus et Causis Morborum, Epist. XVIII, Art. 6, 1760.

degree." Unfortunately, he failed to state definitely just where the aortic constriction in his case existed, or how sharply localized it was. Important early contributions were those of Stoll-Krotowski [6] and Wernicke.[7] The last named found five cases of coarctation diagnosed intra vitam prior to 1875 out of a total of sixty cases reported up to that time. He described the pathologic physiology as follows:

1. The superior intercostals anastomose with the intercostals from the aorta and carry blood into the aorta.

2. The transversalis colli arteries anastomose with the intercostals from the aorta and carry blood into the aorta.

3. The internal mammaries anastomose and carry blood into the intercostals, deep epigastric arteries, etc.

4. The innominate and left interscapular arteries are especially dilated.

Wernicke outlined the clinical syndrome as follows:

1. Collateral arterial circulation.

2. Pulsation in the interscapular area.

3. Dilated intercostal arteries.

4. Murmurs over the anastomotic vessels.

5. Discrepancy between the size of the pulse in the arms and that in the legs.

He also described the two critical periods of the condition which are recognized today, first, the period in infancy when the anastomotic circulation begins to develop and, second, the later myocardial strain imposed by the extensive collateral circulation. He found further that the condition was not incompatible with long life, one patient having attained the age of 92 years. The first American case appears to be that of Hutchinson,[8] though I have not seen the report and it may have been, as many of the early cases were, an instance of hypoplasia of the aorta.

Total obliteration of the aorta occurred in fourteen of 105 cases of coarctation studied by Dickinson and Fenton [9] in 1900, in a case of total obliteration found by them at necropsy and not recognized clinically, the collateral circulation was carried on through the internal mammary and first four intercostal arteries.

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6. Stoll-Krotowski, M.: Stenosis aorte congenita, Berlin, Gustav Lange, 1873.

7. Wernicke, R.: Die Verengerung und Obliteration der Aorta in der Gegend des Ductus Arteriosus Botalli und ihre Diagnose intra Vitam, Berlin, Gustav Lange, 1875.

8. Hutchinson, J. H.: Constriction of the Aorta with Hypertrophy of the Heart, Hosp. Med. Gaz., New York **6**:357, 1879.

9. Dickinson, W. L., and Fenton, W. J.: A Case of Complete Coarctation of the Arch of the Aorta; Necropsy, Lancet **2**:1196, 1900.

An excellent analysis of cases of generalized narrowness of the aorta prior to 1901 was made by Burke,[10] who found seventeen of twenty cases in men, three in women. The average life of his patients was 23.8 years: this is approximately the age described by all writers on the subject as the critical adult age. Most patients die of myocardial insufficiency. Burke found that symptoms had existed for less than one year before death in thirteen cases; for three years in one case; since childhood in five cases, and for an undetermined period in one case. Intermittent claudication occurred in only one case. The symptoms were characteristically rather sudden and were those of typical myocardial insufficiency. There were no blood pressure determinations. In the same year von Minkowski[11] compiled 120 cases of stenosis of the isthmus of the aorta, and reported a case recognized during life, including an excellent clinical description; he found aortic insufficiency with coarctation; blood pressure in the arms 300 +; absence of pulsation in the tibial and peroneal arteries, and barely palpable pulsation in the femorals, which allowed no determination of leg blood pressure. He gives a good description of the collateral circulation, recognizing the prominent pulsation of the transversalis colli arteries, of the dorsal scapular arteries in the interscapular region, and the dilatation of the mammary arteries at the xiphoid; he also described systolic murmurs in the interscapular region near the spine.

Aortic insufficiency is often associated with coarctation; disease of the aortic valves was found in ten of Fawcett's[1] eighteen cases. In many cases (probably a majority of cases) the aortic insufficiency is recognized and the coarctation is passed over. Unfortunately for the clinician, increased vascular pulsation occurs in each condition; when present, such pulsation is probably attributed to the aortic insufficiency, which acts in this way in many cases as a mask for the coarctation.

REPORT OF CASES

CASE 1.—*Coarctation of the Aorta.*

M. P., a single man, aged 35, an Italian laborer, came under observation in the outpatient department of the Johns Hopkins Hospital, May 5, 1908.

The parents were living and well. Of two sibs, one was living and well; one died of unknown cause. There was no history of tuberculosis or cancer.

The patient's general health had been good. He had had an occasional attack of fever, lasting two or three days, since childhood. He thought that he had not had measles, pertussis, mumps, scarlet fever, rheumatic fever, diphtheria, chorea, malaria, typhoid, pneumonia or pleurisy. He had an attack of rheumatism in 1906, being confined to bed for three days. He suffered from a chronic nasal obstruction, and had an occasional sore throat. Adenoidectomy of a large mass of tissue had been performed, Aug. 8, 1913. In November, 1923, he was admit-

10. Burke, Joseph: Ueber angeborene enge des aorten systems, Deutsches Arch. f. klin. Med. **71**:189, 1901.

11. Von Minkowski: Stenose der Aorta an der Einmündungsstelle des Ductus Botalli, München. med. Wchnschr. **48**:1335, 1901.

ted to the hospital for acute laryngitis. In January, 1924, a bilateral resection of the inferior turbinates was followed by bronchopneumonia, from which he made an uneventful recovery.

He had no chronic cough and no dyspnea that was not brought on by hard work, except in 1908, and again in 1913, when he had dyspnea rather easily for considerable periods. He had no bronchitis, sputum or hemoptysis. He suffered considerable palpitation after exertion in 1908. He had no edema and no pleural pain. The appetite and digestion were good. The bowels and habits were regular. He had no hemorrhoids, no abdominal pain, no hematemesis or melena. There were no bladder or kidney disorders except for nocturia (three or four times) which has been present since before 1908. No hematuria and no syphilis were noted; he had had gonorrheal infection without complications twice. The patient had suffered all his life from cramps in the hands and legs.

He did not use tobacco, and beer and wine only in moderation. He did hard labor on a railway in all kinds of weather.

On the first visit to the outpatient department in 1908, the patient complained of pain in the right side of the chest. A year before this he had developed a marked pain in the left side of the chest when he worked hard or ran. He had been dyspneic on exertion during this year, and had noticed palpitation of the heart on exertion. The pain in the right side of the chest was noticed only while working; it was sharp and stabbing in character, causing him to stop work. He had had nocturia four or five times as long as he could remember.

Physical examination in 1908 showed a well nourished boy, of good color; the mucous membrane and the conjunctiva were of good color. The tongue was clean and teeth fair. The pupils were equal and reacted to light and accommodation. The pulse was 72, regular, of good volume and normal tension. The radial artery was slightly thickened. The pulses were equal. The neck was normal in pulsation. The thyroid was normal, and there was visible pulsation above and below the clavicle, especially on the left side, but also on the right. The chest was well developed, the costal angle being under 90 degrees.

In the heart the precordial pulsation was visible in the left second and third intercostal space, and on the right side next the sternum in the second intercostal space. The point of maximum impulse was extremely visible in the fifth intercostal space, about 1 cm. inside the nipple line. There was no thrill, and the boundaries were normal. The first sound at the apex was prolonged, the second was sharp and snapping. In the pulmonic area a prolonged systolic murmur was followed by a snapping second sound. A systolic murmur in the aortic area was transmitted up to above the clavicle, followed by a sharp snapping second sound. There was no thrill in the aortic area and no heaving in the back. In the region of the second dorsal vertebra was the most intense blowing murmur, which corresponded to the systole of the heart. A slight pulsation was felt to the right of this vertebra, but it was not visible except in a certain oblique light. No especial dulness was noted over this area. No shock was felt. The lungs were clear. The abdomen was normal. No sugar or albumin was found in the urine.

The condition was recognized as coarctation of the aorta by Dr. T. McCrae in the outpatient department; the patient was admitted to the hospital, where the following data were obtained:

Blood analysis (1908) showed hemoglobin, 90 per cent; white blood cells, 8,000, and red blood cells, 5,120,000. The differential count was: polymorphonuclear neutrophils, 68.8 per cent; large mononuclears, 5.2 per cent; small mononuclears, 18.4 per cent; transitionals, 5.2 per cent; eosinophils, 1 per cent; nucleated red blood cells, 0.2 per cent; mast, 0.2 per cent, and unclassified, 1 per cent.

Fluoroscopic examination of the chest (1908) by Dr. F. H. Baetjer was negative. The blood pressure (1908) report was: "The pressure taken with the sphygomanometer is equal to if not 5 mm. higher in the femorals than in the brachials." (In view of the subsequent blood pressure findings it seems likely that this note is in error.) The blood pressure (presumably systolic and in the brachial artery) was charted as 175, 155 and 180. An extract from Dr. L. F.

Barker's note (1908) reads: "Fair pulse in left dorsalis pedis artery, also palpable pulsation on the right. Posterior tibials not felt. Distinct pulsation in the radials and temporals. Pulsation in the femorals barely felt Pulse in aorta barely felt on pressure above umbilicus. Popliteal pulse not felt. Distinct pulsation in internal mammary arteries." The tonsils and adenoids were removed.

The urinalysis findings were: light to orange color; specific gravity from 1.011 ao 1.030; acid; sugar, 0; albumin, faint trace on admission, none later Microscopic examination showed a few hyaline casts on admission, none on several examinations later.

A note by Dr. T. McCrae on the hospital record states that the diagnosis of coarctation of the aorta was made in the dispensary and later independently in the hospital. (There was considerable discussion as to whether the patient had aneurysm or stenosis of the aorta.)

July 10, 1913, the patient came to the dispensary with temperature of 100.1 and was admitted to the hospital, where a diagnosis of typhoid fever was made. Before admission Dr. Baetjer made a fluoroscopic examination of the patient and found "no saccular aneurysm. Dilatation of the aorta, comparable to what one would expect to find in a man of 50." While the patient was in the hospital, there was apparently considerable discussion and consultation with the roentgenologic department as to the significance of the curious pulsation and systolic murmur in the left interscapular region. The fever was due to single tertian malarial infection, from which convalescence was uneventful.

May 23, 1917, roentgen-ray examination showed the heart and aorta to be normal. Nov. 26, 1923, the Wassermann reaction was negative; roentgen-ray examination of the heart and aorta was negative; the urine was normal. March 19, 1924, I noted that the chief complaints during recent years had been pains in the arms and legs, especially on straightening them. The patient had suffered over considerable periods with intermittent claudication of the legs, which limited his walking to one or two city blocks at a time, and caused him to give up work.

March 19, 1924, his voice was much stronger. The patient had recently had pneumonia following a nasal operation. He complained now of frequent headaches, beginning in the early morning, and still had cramps in the legs at times but they were not so severe as formerly; he suffered from dyspnea only on hard work.

My examination on this date follows: There was no cyanosis. There was marked pulsation visible in the carotids, subclavians, brachials and radials, also an area in each upper interscapular region in which a visible impulse was present. The femoral pulsation was very small but was palpable on each side. Neither posterior tibial was felt but there was pulsation in each dorsalis pedis artery, slightly reduced. In the heart there was no shock or thrill. The area of dulness was 9 cm. to the left, 5 cm. to the right. There were no murmurs and sounds were normal. There was a well marked systolic murmur heard over the areas of pulsation in the upper interscapular regions on both sides; it was transmitted downward over the descending aorta to about the sixth dorsal vertebra (fig. 1). The pulse was 72, regular and bounding but not collapsing. The systolic blood pressure in the right arm was 180, the diastolic 106; in the left arm, 180 systolic, 98 diastolic. The blood pressure in the right leg (Tycos) and palpation of the dorsalis pedis were 110 systolic; in the left leg, 110.

The Wassermann reaction on several occasions was negative.

Jan. 12, 1924, when the patient had just recovered from bronchopneumonia following a nasal operation, the carbon dioxid in the blood was 58.2 per cent by volume; creatinine, 1.36 mg. per hundred cubic centimeters; uric acid, 3.81 mg. per hundred cubic centimeters; red blood cells, 4,032,000, and hemoglobin, 75 per cent. There was no leukocytosis after recovery.

The blood pressure (presumably from the brachial artery) on this admission was 140 systolic, 80 diastolic, rising gradually with improvement of the patient to 180 systolic, 95 diastolic.

The points of interest in this case were:

1. The presence of intermittent claudication which, though it might be expected because of the interference with the blood supply to points below the arms, is nevertheless rare. Burke found it reported in only one of twenty cases in his series of generalized aortic hypoplasia.

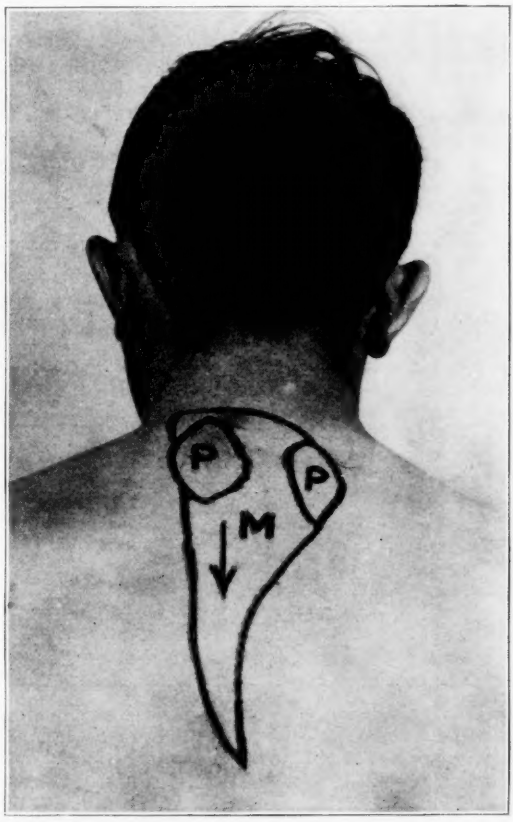

Fig. 1 (case 1).—*P*, areas of systolic, aneurysm-like pulsations (dorsal scapular arteries); over larger zone, *M*, a systolic murmur was heard.

2. The blood pressure was constantly higher in the right arm than in the left. During the seventeen years in which the patient has been under observation the blood pressure in the arms has not changed.

3. The patient worked for years in a railway gang, doing heavy work and being exposed to the weather.

4. Nocturia (two or three times) had been present since childhood.

CASE 2.—*Coarctation of the aorta; aortic insufficiency; arteriosclerosis; hypertension.*

P. S., a white American man, aged 58, a carpenter, engaged in railway work, came under observation in the outpatient department of the Johns Hopkins Hospital, Jan. 20, 1922, and to me, Aug. 22, 1923. He complained of heart trouble.

The father died of heart trouble at 67. The mother died of childbirth. Two sibs were living and well. The family history was negative for cardiorenal disease, tuberculosis, cancer or nervous disease. Three children were living and well; one died in infancy; there was one miscarriage.

The patient had had none of the diseases of childhood; no typhoid fever, no pneumonia, no rheumatic fever. He had had malaria at the age of 25. He had an occasional sore throat. The eyes and ears were good; all the teeth had been removed.

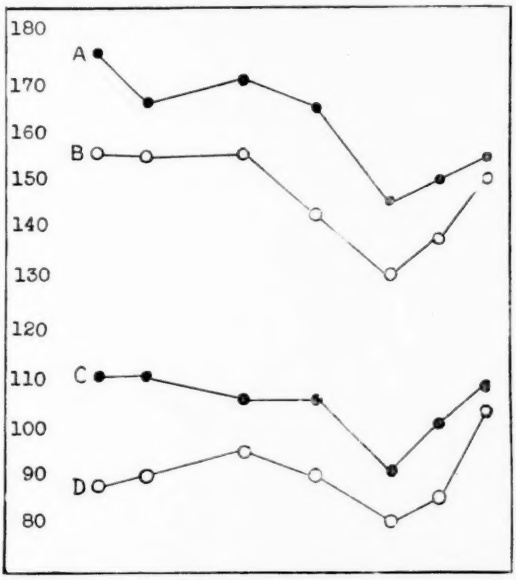

Fig. 2 (case 1).—Systolic and diastolic pressures in arms, illustrating consistently higher pressure in right arm in this case: *A*, systolic pressure in right arm; *B*, systolic pressure in left arm; *C*, diastolic pressure in right arm, and *D*, diastolic pressure in left arm.

In 1919 the patient had a cough for three months, but no hemoptysis. The gastro-intestinal history was negative, except for occasional nausea from smoking. There was no constipation. He had suffered from nocturia (two or three times) for the last twenty-five years. There was no history of primary or secondary syphilis. He had some difficulty in starting the flow of urine. An epithelioma of the wrist was removed in 1916. The patient did heavy outdoor work.

Since 1916 he had had palpitation of the heart and extreme dyspnea, which rendered him unable to work at times.

Physical examination by me, Aug. 22, 1923, revealed that the pain in the left shoulder had ceased and was now merely a sense of numbness. No dyspnea was noted. In addition to the marked pulsation of all the vessels of the upper extremities, the pulsation behind and the systolic murmur over the descending aorta, a very

striking diminution of pulsation in the legs was noted. There was no intermittent claudication. The signs suggested that aortic coarctation should be thought of.

October 24, the patient came in saying that he had no cardiac symptoms. The physical signs were as before. The patient's only complaint consisted of pain over an area the size of a silver dollar in the left supraclavicular fossa, corresponding to the remarkable pulsation that was still there. The pain was always caused by exertion, the patient said. The condition still suggested coarctation of the descending aorta or aneurysm. The roentgen-ray report was: lungs clear; aorta normal, and heart enlarged, particularly the left ventricle.

With the elimination of aneurysm from the diagnostic possibilities, I considered the patient to be suffering from coarctation of the aorta.

March 7, 1924, the patient felt well but still suffered from pain in the left shoulder when he worked, never when he was quiet. At night he "did not have cramps, but the legs were never comfortable on retiring and he was forced to stretch them frequently, or to get up and walk about."

The pupils were round, equal and reacted to light and accommodation. Extraocular movements were normal. The nose was normal. There was a plate in the upper jaw and he had pyorrhea about the few remaining teeth. The pharynx was normal. There were marked generalized arteriosclerosis and tortuous vessels. No gland trouble was noted. The lungs were clear on percussion and auscultation. No thrills or shocks were felt in the heart. The area of dulness was 10.5 cm. to the left, 4 cm. to the right. There was no retromanubrial dulness. The sounds were vigorous. There were soft apical systolic and diastolic murmurs, and a questionable presystolic gallop. The diastolic murmur was maximum in the fourth interspace over the body of the heart and less intense at the pulmonary area and the aortic area; it was heard nowhere behind. It was high pitched and whistling, with a distinct "pressure quality." Behind were marked pulsations as noted in the scapular region and a superficial dilated artery, with blood running from above downward, extending from the apex of the left axilla to the aortic area at the tenth rib. The pulsations in the scapular regions were marked, especially on the left, but were so large and deep that the course of the blood flow could not be determined. There was a pulsation at the eleventh rib on the left near the spine, apparently one of the intercostal arteries. A rather rough systolic murmur was heard over all the area of pulsation behind and along the aorta to the twelfth rib. The abdominal aorta was not palpable. Definite pulsations, not marked, were felt in the femoral, posterior tibial and dorsalis pedis arteries.

The blood pressure (Tycos) in the right arm was 210 systolic, 85 diastolic; in the left arm, 160 systolic, 85 diastolic. The blood pressure in the left and in the right leg was 142 systolic (by palpation) and 80 diastolic (by oscillation).

Roentgen-ray examination revealed the left border 13 cm. and the right border 5.5 cm. from the midsternal line.

March 28, 1924, the blood pressure in the right arm was 170/78; in the left arm, 155/70, and in the left leg, 102/90 (?). In the left leg there was no definite diastolic level, but a systolic level could be auscultated. Nothing was made out in the right leg on auscultation. All determinations on the arms and on the left leg were made with a mercury apparatus and by auscultation.

May 27, 1925, the patient complained of cramps in the legs in the mornings, especially on stretching. He felt quite well. The Wassermann reaction was negative.

An electrocardiogram, Dec. 13, 1922, gave a rate of 65. The rhythm was sinoauricular; the P-R interval measured 0.18 second. The diagnosis was normal sinus rhythm.

The urine was clear and amber, with a specific gravity of 1.02; albumin, 0; sugar, 0. Microscopic examination revealed a few granular casts. There was a considerable number of white blood cells.

CASE 3.—*Coarctation of the aorta; aortic insufficiency.*

W. R., a single, white American man, aged 55, a machinist, first came under observation in the outpatient department of the Johns Hopkins Hospital, Sept. 15, 1916, complaining of nervousness and a queer feeling about the eyes. He thought the kidneys were diseased.

Fig. 3 (case 2).—Areas marked in interscapular region represent limits of forceful, aneurysm-like pulsation (the dorsal scapular arteries, probably anastomosing below with the intercostal arteries from the aorta and thus bridging the stenosis); the tortuous lines represent superficial arteries in which the flow is toward the aorta; these arteries fill readily from either direction but a pulsation is visible in them only when the blood enters from the outer end.

The father was living and well. The mother died of an unknown cause (cancer?).

The patient had measles, chickenpox and mumps as a child. He had no typhoid, but had malaria in 1902. The history was suggestive of arthritis. He had had no pneumonia, no pleurisy and no tonsillitis. He suffered from chronic indigestion,

dry mouth and constipation. He had some fluttering of the heart years before admission, and a chancre seventeen years before. The patient was of a nervous disposition and inclined to worry.

Fluoroscopic examination, Sept. 20, 1916, showed no marked enlargement of the heart. The upper portion of the mediastinum showed a pulsating shadow that extended about 3 cm. outside the right and the left sternal margins. This shadow was pulsating, which is quite characteristic of an aneurysm. Both apexes were cloudy, especially the right, probably owing to the enlargement of the heart back of the aorta. The diaphragmatic movements were normal and there were a few pleural adhesions. The impression was that the patient had a sacculated aneurysm of the transverse arch.

Sept. 15, 1916, the urine was clear and acid, with a specific gravity of 1.007; there were no albumin, sugar or casts. The Wassermann reaction was negative.

Dr. J. H. Pleasants, who first saw the patient, Jan. 9, 1924, considered it to be an instance of coarctation of the aorta similar to case 2, and called Dr. W. T. Longcope into consultation. Dr. Longcope reported that the marked features of the case were the comfort of the patient, who had rather deep, dusky lips and ears, and the extraordinary arterial pulsations above and below the clavicles and in the episternal notch. The pulsations that were below were in the infraclavicular

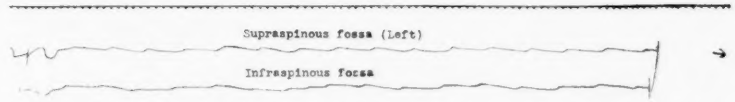

Fig. 4 (case 2).—Pulsation in left interscapular area; these simultaneous tracings show that the pulsation occurs in the supraspinous fossa slightly before it reaches the infraspinous fossa, indicating that the pulsation is progressive from above downward.

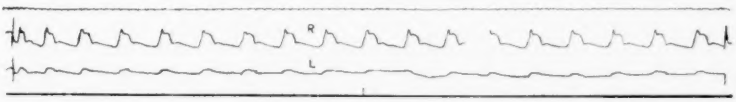

Fig. 5 (case 2).—Simultaneous tracings from two radial pulses; the pulse waves reach the wrist simultaneously but the peak of the wave is delayed in the left radial as compared with the right. These observations bear out those of Stursberg.[21] (The difference in amplitude in the two radial pulses is due to difference in the recording apparatus leading from the two wrists: a similar delay in the peak of the left radial pulse wave occurred when the recording apparatus in the two arms was reversed.)

fossae. There were fairly well marked pulsation in the axillary artery, extraordinary visible pulsation in the upper portion of the back beneath the supraspinous muscles, and tortuous pulsating arteries beneath the angles of the scapulae. These pulsating vessels in the suprascapular regions could be felt like tortuous cords, and similar ones ran horizontally (more or less) from the angles of the scapula. The pulsations in the supraspinous muscles felt superficial and were felt well on deep pressure, when they elevated the wrist. On the right side pulsations extended up into the posterior cervical region. In the lower portion of the axilla were other tortuous pulsating arteries. The retromanubrial dulness was 5 cm. to the right and 3 cm. to the left in the third interspace. The maximum impulse in the fifth space was 11 cm. from the midline. It is particularly noteworthy that with peripheral pulsations there was practically no pulsation beneath the manubrium. The apical impulse was forceful, and the marked tracheal tug was visible. There was a difference between the radial pulses, the one on the

right being more marked. At the apex there was a dull first sound accompanied by a systolic murmur. The second sound was completely obliterated by a high pitched diastolic sound. This double murmur was heard all over the heart, the diastolic being particularly loud along the left sternal border, and heard also at the aortic border. The second sound was not heard anywhere. The first sound was not loud. Over the pulsating area in the back and beneath the clavicles there was a systolic bruit, loudest on the right. In the left supraspinous region was a soft diastolic murmur. The physical signs were those of aortic insufficiency with an enlargement of the left side of the heart and of the aorta, combined with a remarkable peripheral anastomotic arterial condition over the chest which strongly suggested coarctation of the aorta. The fact that the fluoroscope showed only slight enlargement of the aorta supports this view. The murmur might be associated with patent ductus botalli.

Fluoroscopic examination showed a moderate grade of dilatation of the transverse arch of the aorta, probably aneurysm. Unfortunately, this patient left the city and it was impossible to study his condition more thoroughly.

While there were no blood pressure determinations in this case, a difference in size of the radial pulses was noted by two observers, the right pulse being larger than the left.

The case presents practically the same signs as were found in case 2, again with aortic insufficiency. The clinical diagnosis of aneurysm had been made in this case as it had in case 1 before the true condition was recognized.

CASE 4.—*Coarctation of the aorta; Streptococcus viridans septicemia, with recovery.*

A negress entered Johns Hopkins Hospital, Feb. 3, 1925, complaining of weakness and an "awful feeling" in the mouth. She had had nocturia since childhood and one attack of dyspnea and palpitation. There were marked pulsations in the upper extremities and in areas described in the back. A loud systolic bruit was heard in the interscapular area. Feeble pulsation in the lower extremities and high pulse pressure in the arms were noted.

The father died at 80 of old age; the mother died at 45, of an unknown cause. The patient had five sibs, three of whom died in infancy of unknown causes and one at 28 of an unknown cause. One sister and one son were living and well. There was no history of tuberculosis, renal or cardiac disease, cancer, nervous diseases or insanity.

The patient's health had always been good; she had the usual childhood diseases and had pneumonia as a girl. She was operated on in Johns Hopkins Hospital in 1919, a myomectomy being performed; she had postoperative pneumonia. She had had no diphtheria, typhoid, malaria, influenza, scarlet or rheumatic fever or chorea. She was not subject to headache, dizziness or fainting, and had no feeling of fulness in the head; she wore glasses; had rare sore throat; no diplopia; no scotoma, and the nose and ears were negative. The patient had some cardiac palpitation and dyspnea in 1919; both gradually disappeared after the myomectomy. She had no hemoptysis, no chronic cough and no edema. The appetite and the digestion were good, and the bowels were regular. She had had hemorrhoids without symptoms for many years, but no hematemesis, melena or jaundice. The menses began at 16, were regular, of a duration of four or five days, but had ceased with the operation (1919). She had had nocturia once since childhood, but no urinary disturbances. She said she had no genital lesion, and had no symptoms of syphilis. She had acute arthritis of both knees four years before admission, but the joints were neither hot nor very tender. She used alcohol occasionally, but no drug or tobacco.

For four weeks she had had fever, ushered in by a sense of chilliness, which had not returned. She had grown very weak, had no appetite, and had also become somewhat short of breath. The urinary output had decreased, and she felt some urethral burning.

The report of a physical examination by Dr. C. S. Keefer was that the patient seemed comfortable at rest, and had no dyspnea. Examination of the head revealed nothing abnormal; there were no petechiae, but there were numerous

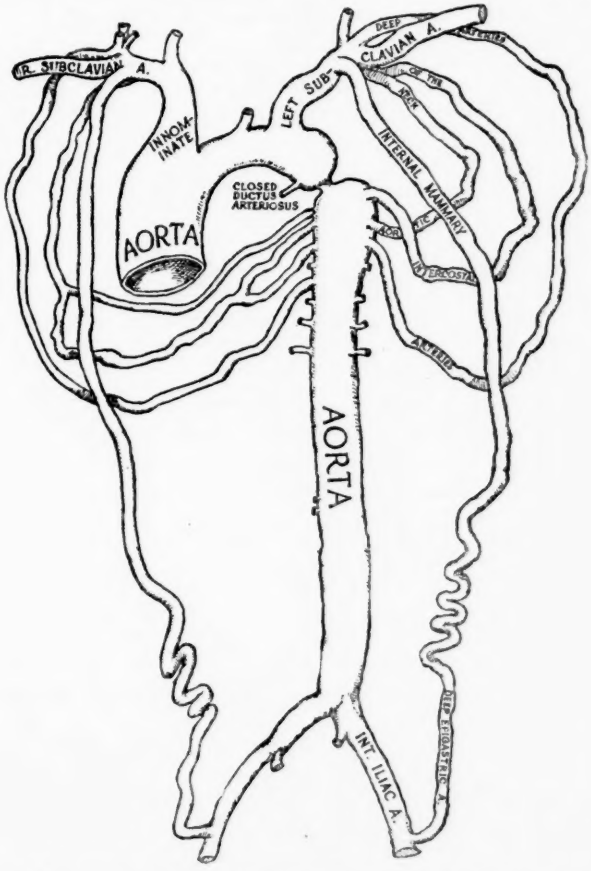

Fig. 6 (after Walshe, from Abbott and Dawson).—Coarctation of the aorta. (This is not drawn to scale; during life the dorsal scapular arteries, included here among the "deep arteries of the neck," are much larger than indicated.)

cherry angiomas over the skin of the chest and back. In the episternal notch, in the carotids and below the clavicles and brachials there was marked visible pulsation. The pulse was bounding and collapsing in type; one could feel this pulsation quite definitely. There did not seem to be a difference in the two arms on palpation. There was no tracheal tug and no general glandular enlargement. The lungs were clear.

The heart was somewhat enlarged. The point of maximum impulse was in the fifth space, just outside the nipple line. No thrills were felt and no shocks. In the back, at the angle of the scapula, just below the infraspinous space there was a definite pulsation on both sides, which felt like a dilated artery on each side. The intercostal arteries could be felt to pulsate in the second and third interspaces anteriorly, as far out as 5 cm. from the midsternal line. The intercostal artery could be felt to pulsate in the second interspace. At the apex the sounds were well heard. There was a distinct systolic murmur, which did not seem to be transmitted from the mitral area but rather from above. Over the base, extending to the right and the left of the sternum and to the episternal notch, there was a loud systolic mumur; it was rough and was followed by a loud second aortic sound. This murmur was louder to the left of the sternum than to the right, and there was a slight increase in retromanubrial dulness. No thrill was felt. In the interscapular space there were loud systolic bruits over the areas in which pulsation has been described in the foregoing. The abdomen was negative. The pulsation in the legs was feeble.

On these data Dr. Keefer felt that the patient had coarctation of the aorta.

The red blood cells totaled 4,088,000; leukocytes, 8,600; hemoglobin, 53 per cent, and the color index was 0.65 per cent. The differential count was: polymorphonuclear neutrophils, 78 per cent; small lymphocytes, 12 per cent; large mononuclears, 5 per cent, and transitionals, 5 per cent.

February 5, an electrocardiogram gave a rate of 80; a sino-auricular rhythm; P-R interval, 0.18 second, and wave T diphasic in Leads I and II. The diagnosis was a normal mechanism, with the levogram predominant.

February 6, the patient was seen by Dr. W. T. Longcope, who concurred in the diagnosis of coarctation of the aorta. The stool was normal; Widal tests and the Wassermann reaction were negative.

A teleoroentgenogram of the heart, made by Dr. F. H. Baetjer, February 5, showed the maximum shadow to the right 4 cm., and to the left 9 cm. The heart was normal. There was a localized dilatation of the arch of the descending aorta, which might involve the subclavian artery.

The blood pressure, both systolic and diastolic, tended to be higher in the left than in the right arm, the reverse of the findings in cases 1 and 2. The figures were as follows: left arm (systolic), 173-230; right arm, 168-210; left arm (diastolic), 85-120; right arm, 80-107; left leg (systolic), 120-150; right leg, 140-162; left leg (diastolic), 72-110; right leg, 75-110.

February 7, *Streptococcus viridans* had been cultivated from the blood. Blood cultures showed this organism to be present in the blood on several occasions, and at discharge, March 30, 1925. The urine was cloudy, with a specific gravity of from 1.006 to 1.032; sugar, 0; albumin, always present; almost constant casts; occasional red cells in the sediment; frequent leukocytes.

June 6, 1924, the patient returned to the outpatient department by request. The blood culture was negative. The patient felt well and had gained in weight. The patient had continued well. In this report we are interested only in the condition of stenosis of the aorta; the case is also of unusual interest because of the *Streptococcus viridans* septicemia, and will probably be reported more fully from that point of view.

COMMENT

Pathologic Anatomy.—The stenosis in the cases under consideration is described as symmetrical and annular, and the portion of aorta involved as rigid. The grade of stricture varies up to complete obliteration (described above). In our series, cases 1 and 4 may be supposed to have a moderate grade of localized coarctation or a fusiform narrowness of the whole isthmus; cases 2 and 3, because of the highly developed collateral circulation, are probably well developed instances

of a sharp stenosis or complete obliteration of the aorta near the entrance of the ductus botalli.

Pathologic Physiology.—This can perhaps be shown best by a diagram prepared by Abbott and Dawson,[12] from Walshe's [13] time honored description. From the clinical standpoint, the most important vessels by far are the dorsal scapular arteries. The circulation in the intercostal arteries from the aorta is reversed, as is that in the deep (inferior) epigastric arteries. There is no necessary cyanosis.

Sex.—The recorded cases show that a majority of instances of coarctation occur in men, but it is not true, as stated by some writers, that the condition is limited to males. Cases in women are reported by Kohn,[14] Weber,[15] Lommel,[16] Focken,[17] Gossage [18] and others. Case 4 of our series was in a woman.

Race.—I have seen no reports of cases in the brown or yellow race, but there is at least one case already on record that occurred in a negro.[19] Case 4 of our series was in a negress. In case 1 the patient was born in Italy. In cases 2 and 3 the patients were born in this country; in case 2 the patient obviously was of Teutonic extraction, and in case 3 presumably so.

Age.—The condition occurs at any age after birth, but it has not been observed in the embryo. The "critical" ages are in early infancy and in the third decade; many patients die during the first critical period, when the collateral circulation is becoming established, while others die in early adult life from myocardial strain. If the patient survives this second strain, he seems to do well. One patient with coarctation lived to be 92 years of age. The ages of our four patients were 35, 58, 54 and 40.

Occupation.—The condition is compatible in some cases with hard labor; patient 1 of our series did hard labor on the street railway, but was forced to take periods of rest. Patient 2 has always worked as a

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13. Walshe, W. H.: Case of Presumed Quasicongenital Coarctation of the Arch of the Aorta, M. Times & Hosp. Gaz. **36**:389, 1857.

14. Kohn, A.: A Case of Dilatation of the Aorta Due to Constriction at the Isthmus, M. Rec. **79**:652, 1911.

15. Weber, R. P., and Price, F. W.: Coarctation of the Aorta in an Adult, with Death Due to the Rupture of an Aneurysm in the Neck, Lancet **2**:692, 1912.

16. Lommel, F.: Ueber Stenose des Aortenisthmus, Med. Klin. **15**:892, 1919.

17. Focken, Ernst: Isthmusstenose der Aorta und Septische Endokarditis, Ztschr. f. klin. Med. **100**:179 (May) 1924.

18. Gossage, A. M.: Coarctation of the Aorta, Proc. Roy. Soc. Med. (Clin. Section) **2**:210, 1909.

19. Weidman, F. D.: Congenital Stenosis (Coarctation) of the Isthmus of Aorta, Proc. Path. Soc. Philadelphia **16**:78, 1914.

laborer, and is still able to do his share of hard work. Patient 3 is listed as a machinist, while patient 4 is a housewife. Patients with this condition are thought not to be fit for general military service owing to their liability to myocardial insufficiency.

History.—We have not found a history of physical insufficiency in childhood in any of our cases. A history of periods of palpitation of the heart was obtained in each of our cases, and three gave a history of definite phases of dyspnea.

Nocturia is a common and, we believe, an important symptom, especially as it usually occurs without evidence of nephritis. No note is found in one case (case 3) as to its presence or absence, but in each of the other three cases it has occurred since childhood, or as long as the patient can remember. It is probably related in some way to the vascular abnormalities and changes in blood pressure.

Symptoms.—The symptoms in most cases are those of myocardial insufficiency—dyspnea, palpitation, edema, etc. Occasionally intermittent claudication occurs (as in case 1), but this is a rare symptom. One of our patients (patient 2) complains of severe cramps in the legs "on stretching" himself in bed in the morning; the cramps occur regularly and cause him to walk about the room to get relief. There may be pain in the interscapular region from the dilated dorsal scapular artery; this symptom called attention to the pulsation and made the diagnosis possible in case 2. In this case the pain occurred only as a result of work.

Signs.—Bilateral pulsation in the interscapular region was present in all four cases. It called attention to the presence of coarctation of the aorta in three cases, possibly also in the fourth. In two cases (cases 1 and 4) this pulsation constituted the outstanding physical sign, and the condition would probably have been overlooked but for its presence. Collateral circulation through the dorsal scapular arteries, carrying arterial blood downward from the deep arteries of the neck into the intercostal arteries and through them into the aorta, causes this bilateral pulsation. Further collateral circulation was well established in cases 2 and 3. The pulsation was clearly visible, as well as palpable, in cases 1, 2 and 3, but in case 4 it was only palpable. A systolic murmur was heard in each case over the areas of pulsation in the back.

Collateral circulation was established in cases 2 and 3 through superficial pulsating arteries in the axillae and subscapular regions, the flow being obliquely from above downward into the intercostal arteries and into the aorta (fig. 3). These arteries presumably drained part of the system of deep arteries of the neck (fig. 6). In case 4 the pulsations of certain intercostal arteries were palpable, indicating that they were probably carrying blood by collateral circuits. An interesting phenomenon is observed when these arteries are stripped of blood by pressure:

on release of pressure, blood enters the artery from either end, but there is pulsation only when the upper end of the artery is patent.

Systolic murmurs seem to be present constantly over arteries carrying blood by collateral channels. A systolic murmur may be present over the whole extent of the thoracic and lumbar aorta (case 2).

Aortic insufficiency, with characteristic secondary changes in the heart, was present in two of our four cases (cases 2 and 3). It is commonly associated with coarctation of the aorta.[1] The lesion of the aortic valves apparently is of neither rheumatic nor syphilitic etiology. Recognized congenital abnormalities of the aortic valves without insufficiency have been noted postmortem. Le Count[20] believes that the aortic valve lesions are probably indications of repair thrombosis and organization of minute ruptures of the aortic leaflets, the result of increased arterial pressure.

Discrepancy between the degree of apparent and palpable pulsation in the upper extremities and that of the legs and abdominal aorta is very striking. This is especially true in cases with associated aortic insufficiency, but there is a definite increase in the visible pulsation of all the arteries of the upper part of the body, even in those patients who have no associated aortic insufficiency. The radial pulse is vigorous and bounding but not collapsing, unless there is associated aortic insufficiency. Pulsation in the brachial, axillary, subclavian and carotid arteries is increased, that in the abdominal aorta and in the arteries of the legs much diminished.

Blood pressure determinations are bizarre. In cases 1 and 2 the blood pressure was consistently higher in the right brachial artery than in the left. We have no records of this feature in case 3. In case 4 the systolic and diastolic blood pressures tended to be slightly higher in the left arm than in the right, though on one occasion it was higher in the right; the discrepancy of pressure readings in case 4 is hardly marked enough or constant enough to be important. The blood pressure in the legs was much lower than that in the arms in all cases in which it was noted (cases 1, 2 and 4).

Difference in the size of the radial pulses was noted in cases 2 and 3; in each of these the right radial pulse seemed larger to the palpating finger. In cases 1 and 4 the radial pulses were noted as being of equal size. Several previous case reports have shown the right radial pulse to be larger than the left.[21] This difference (pulsus differens) has

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been well studied and reported in previous cases of coarctation.[22] These authors found that there was no actual delay of the ascending limb of the radial pulse in the left arm as compared with that in the right, but that the apex of the pulse wave was blunt and retarded in the left radial, as compared with the right. Their findings were comparable to those shown in figure 5. There is an actual delay in the femoral pulse as compared with the radial. Pulsus differens in the radial arteries, due to delay and blunting of the apex of the left radial wave, has been demonstrated by von Ziemssen [23] in two cases in which plaques were found postmortem partly occluding the left subclavian artery. Such a cause is, however, probably lacking in coarctation of the aorta; in the case of Ermann,[24] the orifices of the two subclavian arteries measured the same; in that of Schickhold,[25] in which the left radial pulse was smaller than the right by palpation, the orifice of the right subclavian artery measured 35 mm. while that of the left measured 45 mm.

No doubt the chief difference between the pulse at the two wrists is due to the relative delay of the apex of the left radial pulse wave and its rounded crest. It is unlikely that there is any true difference in total blood supply to the two arms, since no obstruction of the left subclavian artery is found in these cases postmortem, and the pulse pressure in the two arms is not consistently higher in one than in the other arm.

It is difficult to account for the demonstrated difference in form in the two radial pulse waves. It is reasonable to suppose, however, that the proximity of the stenosis to the origin of the left subclavian artery may cause the difference; this is borne out by two considerations: first, the left radial tracing is unusual, while the right radial tracing is of quite natural appearance; second, the obstruction at the isthmus would be likely to cause momentary slowing of the blood stream in the aorta, backward at least as far as the left subclavian artery. Such slowing in the passage of blood past the mouth of the subclavian artery would produce the type of pulse tracing that is obtained from the left radial artery.

In figure 4 is shown a tracing that helped to show that the pulsations in the interscapular region are progressive from above downward. Such a tracing helps to rule out aneurysm.

Roentgenograms are disappointing. One sees a generalized dilatation, usually moderate, of the arch of the aorta. Aneurysm usually is eliminated from the diagnostic possibilities by this method. The site

22. Scheele: Berl. klin. Wchnschr. **7**:32, 1870. Stursburg (Footnote 21, third reference).

23. Von Ziemssen: Ueber den Pulsus und seine Bedeutung bei Erkrankungen des Aortenbogens, Deutsches Arch. f. klin. Med. **46**:285, 1890.

24. Ermann (Footnote 21, second reference).

25. Schickhold (Footnote 21, fourth reference).

of stenosis lies behind the heart, and is so closely flanked to the right by the vertebral column as to make it impossible to inspect this portion of the aorta satisfactorily. The chief value of the roentgen ray is the ruling out of aneurysm.

The electrocardiogram is not modified by stenosis of the aorta.

SUMMARY

1. In the four cases of stenosis of the isthmus (coarctation) of the aorta recognized during life reported, two were thought to be instances of slight stenosis, two of well marked stenosis or total obliteration of the aorta at about the site of the entrance of the ductus botalli.

2. Postmortem reports show that the condition is rarely recognized during life.

3. Coarctation occurs more often in males than in females; it occurs at any age after birth, and is compatible in some cases with long periods of hard physical work.

4. Symptoms that may occur are palpitation, dyspnea, myocardial insufficiency, nocturia, cramps in the legs and intermittent claudication.

5. The signs that may occur are:

(*a*) Bilateral pulsation in the interscapular region. This is the most important physical sign; the pulsation progresses from above downward.

(*b*) Relatively greater pulsation in the upper extremities than in the lower.

(*c*) Pulsating, superficial, collateral arteries, coursing obliquely across the back of the thorax downward toward the spine. Dilated intercostal arteries.

(*d*) Relatively higher blood pressure in the arms than in the legs.

(*e*) Tendency to higher blood pressure in the right than in the left arm.

(*f*) Pulsus differens, due to the relative delay of the apex of the left radial pulse and rounding of its apex.

(*g*) Tendency for the right radial pulse to feel larger than the left.

(*h*) Systolic murmurs over areas of interscapular pulsation, over the collateral arteries, at times over the arch of the aorta anteriorly or over the whole aorta posteriorly.

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THE RÔLE OF INSULIN IN PROTEIN METABOLISM *

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The question of a possible effect exerted by insulin on protein metabolism is of considerable significance both from a metabolic and a clinical standpoint. Intermediate carbohydrate metabolites are capable of synthesis together with nitrogenous compounds into protein. The well known sparing effect of carbohydrate on protein breakdown is probably due in part to such anabolic processes, as isodynamic amounts of fat fail to exert this influence. If, therefore, it could be shown experimentally that insulin increased this sparing function of carbohydrate, the conclusion would be near that this hormone probably had played a definite rôle in the synthesis of protein from carbohydrate.

To test this hypothesis, a short series of metabolic experiments were conducted in an institution especially equipped for metabolic patients, insuring accuracy in the specimen collections and in the preparation, weighing and recording of the food. The fluid intake was distributed equally during the experimental periods. Normal human subjects were placed on a fixed, weighed, mixed diet or on a practical fast for varying periods. The amount of protein sparing for a given day or period was ascertained by giving known amounts of carbohydrate. Later the effect of the addition of insulin to such glucose intake was ascertained. Urinary nitrogen and glucose were determined or tested for; and in the blood, glucose, urea nitrogen and nonprotein nitrogen were determined with standard methods of analysis.

RESULTS

Insulin and glucose were found to cause additional sparing of protein over glucose alone in each of six experiments carried out on five different subjects. Therefore, the series was not extended.

The total urinary nitrogen was reduced in the twelve day metabolic test from the control average of 10.83 Gm. to 10.58 Gm. by glucose and to 9.36 Gm. by insulin and glucose (average of experiments 1 and 2). As was to be anticipated in view of the moderate amounts of glucose administered, the depressant effect on the total nitrogen was not large on the glucose days. It seemed significant, however, that the combination of insulin and glucose effected an average

* From the Scripps Metabolic Clinic, La Jolla, San Diego, Calif.

sparing of 13.6 per cent as compared to the average control nitrogen. The descrease ascribable to the superimposed effect of insulin was 11.5 per cent of the nitrogen output of the glucose days.

For the purpose of further simplification, the succeeding experiments (experiments 3, 4, 5 and 6) were conducted for shorter periods on subjects practically fasting, except for small amounts of carbohydrate given during the experimental periods. The results afford a direct comparison of the action of carbohydrate on the otherwise fasting metabolism with the same effect plus insulin administration. To avoid any possible influence of one experimental period on another, they were never consecutive.

TABLE 1.—*Nitrogen Sparing Experiments (1 and 2)*

M. S., a male, weighing 64 Kg., was placed on a daily diet of 111 Gm. of carbohydrate, 70 Gm. of protein and 191 Gm. of fat. September 17, 21 and 22, 75 Gm. of glucose was given; September 18, 85 Gm., and September 18 and 22, 40 units of insulin (U 40). There were no reactions.

	Date—September, 1924											
	13	14	15	16	17*	18†	19	20	21*	22†	23	24
Total 24 hour urine nitrogen, Gm.....	10.60	10.41	11.14	10.00	10.50	9.11	11.40	12.25	10.67	9.61	10.35	10.52

* Glucose given.
† Glucose and insulin given.

TABLE 2.—*Nitrogen Sparing Experiment (3)*

H. B., a female, weighing 51 Kg., was given no food on the experiment days until 1 p. m. Glucose, 60 Gm., was given at 8 a. m.; 20 Gm. at 10 a. m.; 30 units of insulin (U 40) at 7:30 a. m. Date, October, 1924.

		Period					
		8 p.m.-6 a.m. Aver. 2 Hr.	6-8 a.m.	8-10 a.m.	10 a.m.-12 n.	12 n.-2 p.m.	Total
Total urine nitrogen. Gm.	Glucose, day	0.60	0.51	0.85	0.81	0.42	5.61
	Glucose and insulin, day	0.54	0.47	0.71	0.67	0.33	4.89

In the entire series of six experiments, on the insulin-glucose day or period the nitrogen output was decreased as compared to the glucose day. In five of the six experiments the additional drop in the nitrogen, due to insulin, represented from 9.93 to 13.79 per cent of the nitrogen output obtained under the influence of glucose alone. In experiment 5, however, only a 4 per cent decrease was noted. Inquiry disclosed that this subject, who showed the lowest per kilogram nitrogen excretion of the series, was accustomed to subsist almost on a purely carbohydrate diet. This fact probably influenced the experimental result.

Nitrogen partitions at two hour intervals were carried out in experiments 3 to 6, inclusive, without definite results. They are recorded in the protocols.

TABLE 3.—*Nitrogen Sparing Experiments (4, 5 and 6)*

Experiment 4: M. A., a female, weighing 59 Kg. Experiment 5: E. A., a male, weighing 69 Kg. Experiment 6: D. K., a female, weighing 57 Kg.

Date, October-November, 1924		Period: 8 p.m.-6 a.m. Aver. 2 Hr.	6-8 a.m.	8-10 a.m.	10 a.m.-12 n.	12 n.-2 p.m.	2-4 p.m.	4-6 p.m.	6-8 p.m.	Total 24 Hr.	Glucose and Total Food, Gm.	Insulin (U 40)
Experiment 4												
Total urine nitrogen, Gm.	Glucose, day	0.87	0.63	0.92	1.05	0.74	0.61	0.44	0.44	9.21	Each day: 9 a.m., glucose, 60; 10:45 a.m., glucose, 30; 12 n., carbohydrate, 33; protein, 0.8; fat, 2.4	8:30 a.m. 32 units
	Glucose and insulin, day	0.82	0.26	0.69	0.91	0.41	0.49	0.69	0.58	8.16		
Experiment 5												
Total urine nitrogen, Gm.	Glucose, day	0.69	0.87	0.53	0.89	0.71	0.49	0.42	0.38	7.76	Each day: 9 a.m., glucose, 70; 10:45 a.m., glucose, 30; 12 n., carbohydrate, 33; protein, 0.8; fat, 2.4	8:30 a.m. 36 units
	Glucose and insulin, day	0.63	1.07	0.60	0.72	0.33	0.43	0.48	0.59	7.45		
Experiment 6												
Total urine nitrogen, Gm.	Glucose, day	0.83	0.49	0.88	1.04	0.90	0.49	0.47	0.39	8.83	Each day: 8 a.m., glucose, 50; 10 a.m., glucose, 20; 1 p.m., carbohydrate, 33; protein, 0.8; fat, 2.4	7:20 a.m. 32 units
	Glucose and insulin, day	0.70	0.50	0.56	0.74	0.62	0.67*	0.46	0.38	7.44		
	Glucose, day	0.62	1.31	0.74	0.99	0.50	0.48	0.66	0.65	8.43		

TABLE 4.—*Blood Studies (Experiments 1-5)*

Date, September-November, 1924		Time (Hours) After Feeding Glucose: Experiment 1			Experiment 2				Experiment 3				Experiment 4				Experiment 5			
Mg. in 100 Cc.		Fast	¾ Hour	2 Hours	Fast	1 Hour	1¾ Hours	2½ Hours	Fast	½ Hour	1 Hour	2 Hours	Fast	1 Hour	1¾ Hours	3 Hours	Fast	¾ Hour	1¾ Hr.	3 Hr.
Glucose	Glucose, day	95	124	76	94	129	97	98	111	175	157	112	100	127	139	136	87	122	83	88
	Glucose and insulin, day	91	121	51	95	125	57	59	114	106	80	54	98	165	88	72	85	80	42	52
Urea nitrogen	Glucose, day	17.8	16.0	17.3	19.6	15.6	18.0	15.6	18.1	19.3	20.1	18.4	13.9	15.0	12.5	11.5	14.7	15.9	15.0	15.6
	Glucose and insulin, day	16.7	17.3	16.0	16.8	16.5	14.2	16.2	17.9	16.4	15.2	13.5	13.6	14.3	14.4	12.0	15.4	14.6	14.3	13.5
Nonprotein nitrogen	Glucose, day	45.7	40.0	43.2	40.0	35.9	37.0	37.2	42.0	40.3	40.5	39.8	35.3	39.5	41.3	33.3	36.5	34.8	35.5	33.8
	Glucose and insulin, day	44.0	41.6	43.0	38.8	37.6	35.0	37.2	41.6	40.0	37.8	34.3	35.3	37.5	34.2	35.3	35.8	34.1	32.6	31.0

Results of the Blood Experiments.—The urea nitrogen and nonprotein nitrogen levels were followed in the blood, the protocols affording comparisons between the fasting state, the glucose and insulin-glucose periods. No consistent or very marked influence was noted in the glucose periods, the fluctuations being within the range of normal variations. After the combination of insulin and glucose, a decrease was usually found; the average fall, as compared to the fasting level, being 8.3 per cent for urea nitrogen and 5.4 per cent for nonprotein nitrogen.

Since the work of Haldane, Kay and Smith [1] has shown insulin to cause an increase in blood volume, the drop in the foregoing blood constituents after insulin may have no further significance than a dilution effect. These results cannot, therefore, be interpreted as dependable evidence for a possible removal of urea nitrogen and nonprotein nitro-

TABLE 5.—*Blood Study (Experiment 6)*

Date, November, 1924		Time (Hours) After Glucose Feeding				
Mg. in 100 Cc.		Fast	¾ Hour	2 Hours	5 Hours	8 Hours
Glucose	Glucose, day	82	...	74	82	88
	Insulin and glucose, day	82	...	30	61	85
Urea nitrogen	Glucose, day	12.9	...	12.3	13.2	14.6
	Insulin and glucose, day	13.9	...	25.0	13.6	14.5
Nonprotein nitrogen	Glucose, day	34.0	...	36.2	33.7	37.6
	Insulin and glucose, day	34.8	...	45.5	32.9	37.4

gen coincident and together with glucose from the blood to the tissues for synthetic purposes. In one instance, experiment 6, a definite increase of urea and nonprotein nitrogen was observed to accompany deep hypoglycemia, possibly a toxic manifestation.

It seemed advisable to administer substantial amounts of insulin in these experiments. In such work with normals, it was found practically impossible to avoid insulin reactions. In spite of rather profound hypoglycemia noted in several instances, the reactions went no further than perspiration and weakness. The subjects remained perfectly quiet. Therefore, it seems unlikely that toxic phenomena or increased muscular activity has perceptibly influenced the nitrogen urinary excretion, particularly when one recollects that a toxic effect on protein metabolism usually results in a loss of cell substance, hence an increase rather than the observed decrease in the nitrogen output.

1. Haldane, J. B. S.; Kay, H. D., and Smith, W.: J. Physiol. **59**:193 (Oct.) 1924.

COMMENT

There are but three possibilities concerning the action of insulin according to Macleod's [2] logical analysis, as follows: Insulin can cause hypoglycemia, either by (1) direct action on the blood; (2) blocking of glycogenolysis in the liver or muscles, and (3) acceleration of glucose consumption in tissues.

1. Direct action on the blood can be excluded by the negative results of glycolysis experiments.[3] Yet according to Winter and Smith [4] it is still possible that insulin might affect stereochemical changes in the blood glucose molecule, rendering it more labile. The pertinent experimental evidence and conclusions supporting this interesting hypothesis have, however, failed of substantiation.[5]

2. Blocking of glycogenolysis in the liver would cause hypoglycemia if consumption of glucose in tissue were normal. This view is inacceptable as, after insulin injections, glucose disappears from blood of hepatized animals at the same rate as in normal animals. When insulin is given to sound animals, glucose disappears indeed much more rapidly than in the case of hepatized animals without insulin.

3. By exclusion, therefore, the action of insulin must be on the tissues, and insulin hypoglycemia must ensue as a result of the demand for glucose set up by insulin in the tissues.

It becomes of great importance to determine whether the liver is the chief seat of insulin action, on account of the rôle played by this organ in carbohydrate metabolism. Recent important perfusion experiments by Burn and Dale [6] with hepatized and eviscerated animals demonstrate that the liver cannot be of prime importance in insulin metabolism, as the heart and skeletal muscles are largely responsible for disappearance of glucose under insulin influence. Previously the liver was shown to be unessential to the action of insulin by Mann and Magath,[7] as was also the case with the brain as demonstrated by Olmsted and Logan.[8] Hepburn and Latchford [9] and also Thalhimer have noted the same in studying heart preparation; also Cori, Cori and Goltz [10] and Lawrence [11] in study of perfused limbs. This evidence does not dis-

2. Macleod, J. J. R.: Physiol. Rev. **4**:21 (Jan.) 1924.
3. Eadie, G. S.; Macleod, J. J. R., and Noble, E. C.: Am. J. Physiol. **65**:462 (Aug.) 1923.
4. Winter, L. B., and Smith, W.: Brit. M. J. **1**:711 (April 28) 1923.
5. Eadie, G. S.; Macleod, J. J. R., and Noble, E. C.: Am. J. Physiol. **72**:614 (May) 1925.
6. Burn, J. H., and Dale, H. H.: J. Physiol. **59**:165 (Oct.) 1924.
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9. Hepburn, J., and Latchford, J. K.: Am. J. Physiol. **62**:177 (Sept.) 1922.
10. Cori, G. T.; Cori, C. F., and Goltz, H. L.: J. Pharm. & Exper. Therap. **22**:355 (Dec.) 1923.
11. Lawrence, R. D.: Brit. M. J. **1**:516 (March 22) 1924.

prove, however, that the liver is equally concerned with all the organs in the function of insulin, which indeed is likely.

As the action of insulin cannot depend on a special function of the liver, it is even possible that the effect of insulin on glycogen may be secondary and only incidental to its general function in the tissues involving a demand for glucose. Certainly insulin does not promote glycogen formation in the liver of normal animals,[12] and causes glycogen already deposited in normal muscles and liver to decrease in amount.[13] The loss of glycogen is evidently due to the glucose hunger of the tissues.

The Fate of Glucose Metabolized by Insulin.—The following facts have been ascertained from recent animal respiratory work with insulin. When muscular activity and other disturbing factors are properly controlled, the oxygen intake is usually transiently and slightly increased or even decreased as a result of insulin action. The respiratory quotient may become a little elevated or remain about unity. These results taken as a whole indicate that oxidative processes are initiated by insulin; but the amount of oxygen thus absorbed is insufficient to account for disappearance of much of the sugar through combustion. Conversion into fat can be excluded in all but a few instances. The metabolism is changed quantitatively in that more carbohydrate enters into the process. Disappearance of such glucose is best accounted for by its conversion into some unknown substance, neither fat nor carbohydrate.[14] The relation of lactic acid to glycolysis by insulin has not been definitely determined. The diminution of blood phosphates as a result of insulin action is likewise accounted for by an *oxidative synthetic process* according to Winter and Smith [15] and by Brugsch.[16]

THE RELATION OF INSULIN TO PROTEIN METABOLISM

Experimental data are scanty as attention has been hitherto focused on the relation of insulin to diabetes, hence to carbohydrate metabolism. Decreased nitrogen output in a dog on high protein diet and insulin has

12. McCormick, N. A.; Macleod, J. J. R., and O'Brien, M. K.: Tr. Roy. Soc. Canada **17**:57, 1923. Dudley and Marrian: Biochem. J. **17**:435, 1923.

13. Dudley and Marrian (Footnote 12, second reference). Brugsch, I. T.; Benatt, A.; Horsters, H., and Katz, R.: Biochem. Ztschr. **147**:112, 1924.

14. Krogh, A.: Deutsche. med. Wchnschr. **49**:1321 (Oct. 19) 1923. Eadie, G. S., and Macleod, J. J. R.: Am. J. Physiol. **64**:285 (April) 1923. Burn and Dale (Footnote 6). Brugsch, T.: Deutsche med. Wchnschr. **50**:491 (April 18) 1924.

15. Winter, L. B., and Smith, W.: J. Physiol. **58**:327 (March) 1924.

16. Brugsch (Footnote 14, fourth reference).

been reported by Macleod and Frank N. Allan.[17] Protein sparing as a result of insulin administration in diabetic cases has been noted by Fitz, Murphy and Grant.[18] In their insulin dosage studies, certain of Olmsted and Kahn's[19] protocols, for example case 6, show definite protein sparing in diabetes as a result of insulin administration. The experimental evidence submitted in the present article demonstrates that, in normal human subjects, the protein sparing action of carbohydrate is increased by insulin.

CARBOHYDRATES AND PROTEIN SYNTHESIS

Before discussing the possible relation of insulin to protein it seems expedient to emphasize that carbohydrate metabolites probably *normally* enter into protein synthesis. The immense pertinent data can be but alluded to here. A critical analysis of the same up to 1918 was made by one of us.[20] Much confirmatory evidence has been added thereafter; for example, the synthetic possibilities of the ketonic aldehydes derived from carbohydrates are now known (Dakin and Dudley).

The theory that carbohydrate or its metabolites enters into the synthesis of protein was supported by Kassowitz, Paton and Cathcart among many others on the basis of the protein sparing action of carbohydrate, as has been demonstrated by Landergren,[21] Cedereutz,[22] Cathcart,[23] Kayser[24] and Ringer.[25] It has thus been fairly established that, under both experimental and normal conditions in animals and man, (1) carbohydrate is necessary for the retention of nitrogen; (2) carbohydrate is so urgently required that, should it be deficient in the diet, tissue protein is catabolized to supply carbohydrate metabolites even when the dietary contains an adequate amount of protein and fat for ordinary metabolic and fuel requirements; (3) a purely dynamic hypothesis, such as simple fuel replacement, fails to account for this specific function of carbohydrate.

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20. Janney, N. W.: New York M. J., May 4 and 11, 1918.
21. Landergren, E.: Skandin. Arch. f. Physiol. **14**:112, 1903.
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23. Cathcart, E. P.: J. Physiol. **34**:311, 1909-1910; The Physiology of Protein Metabolism, London, 1912.
24. Kayser: Du Bois Arch., 1893, p. 371.
25. Ringer, A. I.: J. Biol. Chem. **12**:431, 1912.

Ingested amino-acids are immediately deaminized very completely as shown by Levene and others. The older view that the amino-acids of the food are directly incorporated as such into new protein is no longer tenable. With few exceptions it may be regarded as practically demonstrated that tissue amino-acids, hence protein, may be freely synthesized from the split products of ingested animo-acids, carbohydrate metabolites and various nitrogenous compounds. As a classic example, alanine has long been known to be formed in perfused liver from glycogen and ammonium chloride.[26] Much evidence has now accumulated supporting the modern point of view that ingested and body protein, carbohydrates and fats undergo catabolism into various intermediary metabolites which are continuously built by a *process of selective synthesis* into higher products, including protein, which is required by the wear and tear of living tissues. This is the only possible explanation of the remarkable and elaborate experiments of Osborne, Mendel and co-workers, who demonstrated the maintenance and even propagation of carnivora (mice) on a diet, the nitrogen of which was supplied by a single amino-acid.

INSULIN AND PROTEIN SYNTHESIS

If we accept, then, that carbohydrate metabolites probably enter into protein synthesis, what rôle, if any, does insulin play in this process? Present evidence, it must be admitted, is mostly indirect and presumptive.

To recapitulate, protoplasmic organs, particularly the muscles, show a remarkable affinity for carbohydrate, especially for glucose. The need for carbohydrate is so vital that a glycogen reserve is maintained by a special metabolism against such need. All the protoplasmic organs, and no special one, are the seat of activity of insulin. Therefore, insulin action is a general one on protoplasm. Permeability of cells is markedly increased by insulin.[1] The breakdown of protein, in animals [17] and in normal men and women (demonstrated by experiments in this article), can be inhibited by insulin. Large amounts of glucose disappear in the tissues under the influence of insulin, and in careful respiratory quotient experiments, such glucose cannot be accounted for by combustion alone.[27] As direct evidence that insulin actively aids protein synthesis, it seems that we have only the important observation of Gey and Thalhimer,[28] who, using Carrel's tissue growing methods, obtained a much greater growth of such cultures on addition of insulin and glu-

26. Knoop, F.: Ztschr. f. physiol. Chem. **67**:489, 1910. Embden, G., and Schmitz, E.: Biochem. Ztschr. **29**:423, 1910.

27. Macleod (Footnote 2), Burn and Dale (Footnote 6).

28. Gey, G. O., and Thalhimer, W.: J. A. M. A. **82**:1609 (May 17) 1924.

cose than could be obtained by glucose alone. Further experimentation of this kind is urgently indicated.

However deficient the foregoing evidence as a whole may be regarded, yet it has a decided value from the standpoint of exclusion. Thus it is impossible to account for the disappearance of glucose in animal tissues without acceptance of the theory that it is transformed into material no longer having the chemical characteristics of glucose and involving oxidative processes.[29] Neither fat nor glycogen nor carbohydrate metabolites, such as lactic acid, are found to accumulate in sufficient quantity in such periods of active metabolism to account for the mass of such disappearing glucose. Recollecting, then, the constant need of replacement, repair and regeneration of old protein, as well as growth of new, and the fact that such glucose utilization is now demonstrated to be a function of insulin, *it seems possible that carbohydrate metabolites are synthesized into the protein molecule by the aid of insulin.* This conception leaves the question open as to whether such actual syntheses are ultimately a function of the tissue enzymes or of insulin. Insulin's rôle may be limited to the preparation of certain labile intermediary carbohydrate metabolites indispensible for protein synthesis.

INSULIN AND PROTEIN METABOLISM IN DIABETES

According to evidence presented and discussed in this article, the sparing action of insulin on protein metabolism takes place in both the normal and the diabetic subject, which would indicate that so far as the effect of insulin is concerned, there is no appreciable difference in either case. The chief point of divergence seems to lie in the deficient supply of insulin in diabetes, and the disastrous effect of this lack on protein and possibly also on fat metabolism. The increase in protein breakdown in severe diabetes was formerly regarded as due to fuel purposes alone, i. e., to replace carbohydrate incapable of combustion, or in the second place as due to acidosis poisoning. It seems, however, that this process is really more complicated. It is well to recollect that body protein, constituting vital tissue, is never broken down for fuel if sufficient carbohydrate or fat is present. Yet in the preinsulin treatment of diabetes, the isodynamic replacement of carbohydrate, fuel that could not be burned, with fat failed to prevent protein breakdown in the severest diabetes, precisely as in Landergren's classical protein sparing experiments on normals. As Woodyatt has clearly shown, part of this protein destruction may take place in order to supply carbohydrate should this be deficient in the diet. The diabetic metabolism here reacts just the same as the normal, for in either a

29. Macleod (Footnote 2). Burn and Dale (Footnote 6). Brugsch (Footnote 14, fourth reference).

certain amount of carbohydrate or carbohydrate metabolites seems indispensable. If not contained in the food, protein must be broken down to supply the deficiency. The acidosis and protein breakdown of diabetes may be regarded as strictly analogous to that of inanition. In both conditions there is a shortage of constituents of protein *Bausteine,* in the case of diabetes through failure of the insulin supply; in inanition, through failure of the food supply. Increased protein catabolism would be due in either case partly for fuel purposes and partly to supply the intermediary products for synthetic repair processes in other protoplasm of prime importance, such as the heart and the brain. It is well to keep in mind the conception of "protein starvation in diabetes," a type of starvation so severe that no ingenious balancing during preinsulin therapy of rations could withstay its lethal termination in severe cases.

The relation of acidosis to this "anabolic conception" of diabetic metabolism requires mention. Without attempting to launch far into the tempestuous sea of intermediary metabolism, the following seems clear. In diabetes, the catabolism of protein and fat is accompanied by the excretion of B-oxybutyric acid and diacetic acid, among other products. Giving of glucose may partially remove such acid products, but insulin and glucose given together promptly clear up such so-called acidosis. It seems, then, logical to conclude that insulin aids either in the oxidation of these intermediary products or in their removal, or in that of their precursors, by transformation into other material, probably by synthesis with intermediary carbohydrate products. Acidosis in diabetes had best be defined as demonstrable signs of protein starvation, or the blocking of fat metabolism, rather than a clinical state, the so-called acidosis poisoning. The weak point in the acidosis poisoning theory has always been the fact that while most patients in diabetic coma enter this condition with profound acidosis, yet there are others who after slight trauma, infections and the like become comatose with but few demonstrable signs of acidosis. Both of these types may show a prelethal rise of nitrogen metabolism.

It is notable that, if given in time, insulin saves cases in both these categories. If we keep in mind the intimate relation of carbohydrate and protein metabolism, it seems possible that the symptoms of diabetic coma may develop just as in other terminal comas induced by such conditions as starvation, poisoning and sepsis, as a result and expression of extensive cellular death. Death of the affected organism will ensue if repair and regenerative processes fail to recuperate the loss promptly. Thus it seems more reasonable to account for diabetic coma as an end-result of protein starvation, rather than to overforce the acidosis etiology in the face of diametrically opposed laboratory and clinical data. Certainly the failure of carbohydrate administration alone, or of

insulin with insufficient carbohydrate, suggests an intimate relation between insulin, carbohydrate and cellular metabolism. It seems particularly significant that cessation of protein breakdown ushers in the clinical recovery of such coma cases.

Certain other clinical observations would tend to support such a point of view. For example, diabetes is particularly severe in children. Under preinsulin treatment, they tended to grow slowly even when supplied with sufficient food calorically. Normal growth, which is but the outward and visible sign of active protein synthesis, is rapidly restored with insulin, as is well known. In diabetic adults, resistance to infection and fatigue is frequently observed to result from the administration of a few units of insulin, even when no caloric increase of diet had been instituted.

USE OF INSULIN IN NONDIABETIC CONDITIONS

It is believed that the data reported in this article afford a logical basis for the thorough trial of the insulin-carbohydrate treatment in nondiabetic conditions involving strain on the protein tissues. Such conditions would be prolonged infections, sepsis, malnutrition, nondiabetic toxic and comatose states; also trauma, particularly when accompanied by acidosis. Some encouraging steps have already been taken in this direction, particularly in the treatment of operative trauma and the toxemia of pregnancy.[30]

SUMMARY AND CONCLUSIONS

1. *The seat of activity of insulin is in the protein tissues.* Data from the literature establish that the seat of insulin activity lies in the tissue cells of the entire organism. Large amounts of glucose disappear in the tissues during insulin activity. Such utilization of carbohydrate can be accounted for only by conversion into material other than glucose, and not by total combustion alone.

2. *Protein sparing by carbohydrate is increased by insulin.* Experimental evidence is recorded demonstrating, in normal human subjects, that insulin and carbohydrate spare more protein than does carbohydrate alone. As protein sparing by carbohydrate is probably an expression of protein synthesis from carbohydrate metabolites, the data here reported would indicate that insulin functions in aiding protein synthesis from carbohydrate, probably by providing necessary metabolites. Hence, insulin has an anabolic (protogenic) as well as a catabolic (glycolytic) function.

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30. Thalhimer, W.: Surg. Gynec. Obst. **39**:237 (Aug.) 1924. Fisher, D., and Snell, N. W.: J. A. M. A. **82**:699 (March 1) 1924.

3. *Diabetes may be a result of deficient protein anabolism.* The foregoing data indicate that the ultimate disturbance in diabetic metabolism may be deficiency in the replacement, regeneration and repair of protoplasm due to the lack of carbohydrate metabolites normally provided by the insulin. This hypothesis affords a rather attractive explanation for diabetic metabolism and symptomatology as follows:

Diabetic metabolism is characterized by protein loss, acidosis, adiposity and lipemia, in addition to glycosuria and hyperglycemia.

In the severest diabetes, untreated with insulin, the body protein loss continues in spite of replacement, in the diet, by food protein and fat of the inutilizable carbohydrate. Protein loss must therefore be due to other than dynamic reasons alone. Such a specific breakdown of protein can be adequately explained as resulting from a lack of normal protein regeneration from indispensable carbohydrate metabolites supplied, in health, by insulin.

Such protoplasmic starvation, if prolonged, could lead to extensive cellular exhaustion and ultimately to death of the organism. Diabetic coma may be the clinical expression of such changes. Strain on the protein tissues would hasten the onset of such coma, which may be accompanied by a prelethal rise in the nitrogen output. Acute infections, trauma and pregnancy, common causes of diabetic coma, exert strain on the protein tissues.

The acidosis theory of diabetic coma is untenable, as coma may intervene with but mild acidosis. An increase of acid bodies results from protein loss and abnormal fat metabolism, which again may possibly be due to lack of certain specific carbohydrate cleavage products normally supplied through the functioning of insulin. "Acidosis" is to be regarded as an effect rather than a cause of this process. Diabetic adiposity and lipemia may possibly arise from fatty carbon chains by aldol condensation of carbohydrate metabolites normally entering into protein synthesis.

Impairment of protoplasmic repair processes can likewise account for the proneness to infection and slow healing exhibited by diabetic tissues, retardation of growth in young diabetic patients, and muscular weakness in diabetic patients even on balanced diets.

The return to normal of the diabetic patient treated by insulin would indicate that all the various metabolic and clinical manifestations of diabetes are due to one general cause, presumably the failure of utilization of carbohydrate. This "anabolic conception of diabetes" likewise recognizes one general cause, failure of utilization of supply of carbohydrate metabolites necessary for protein regeneration. The loss of carbohydrate fuel fails to account adequately for the total metabolic and clinical manifestations of diabetes.

4. *Metabolism of inanition.* The metabolism of inanition may be explained on an analogous basis. The lack of carbohydrate metabolites, as well as protein, in the food produces results similar to the lack of insulin in diabetes, namely, protein loss in addition to dynamic causes, acidosis and prelethal rise in nitrogen excretion. Administration of carbohydrate but not fat reduces the protein loss to a minimum, as insulin is present in abundance.

5. *Insulin-carbohydrate therapy in nondiabetic conditions.* Experimental support is herewith afforded for the extension of insulin therapy to various nondiabetic conditions, characterized by protoplasmic strain on tissues, such as inanition, trauma and sepsis.

THE RELATIVE IMPORTANCE OF THE SYSTOLIC AND THE DIASTOLIC BLOOD PRESSURE IN MAINTAINING THE CORONARY CIRCULATION *

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G. H. MILLER, M.D.
AND
V. C. GRABER, M.D.
IOWA CITY

It is generally known that the coronary circulation is greatly influenced by changes in blood pressure. This was well illustrated by the experiments of Markwalder and Starling.[1] In some instances they obtained 100 per cent increase in the rate of coronary flow by elevating the blood pressure from 80 to 110 mm. of mercury. The relative importance of the two phases of the blood pressure in maintaining the coronary circulation, however, has not been determined. In the study of the coronary circulation in the tortoise, the blood was observed to flow very rapidly during the diastolic phase, whereas during the height of the systolic period the smaller arteries were closed and the blood came to a standstill in the larger vessels.[2] It would thus seem that the rate of coronary flow is to a large extent dependent on the height of the diastolic pressure. It is therefore not improbable that the disturbance in the coronary circulation resulting from the decreased diastolic pressure in aortic regurgitation and arteriovenous aneurysm may be partially responsible for the increase in the size of the heart, and later the onset of cardiac failure. The observations of Cazamian [3] and Leriche,[4] in which a decrease in the size of the heart was noted following the repair of arteriovenous aneurysm, favors this conception. In the case reported by the latter there were, in addition to the increase in the size of the heart, clinical manifestations of cardiac failure. Following the operation the signs of cardiac failure disappeared and the heart returned to the normal size.

Lewis [5] has shown that the arterial phenomena in arteriovenous aneurysm and aortic regurgitation, which are fundamentally dependent on the decrease in the diastolic pressure with an increase in the pulse

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* From the State University of Iowa College of Medicine.
* Read before the American Society for Clinical Investigation, Atlantic City, N. J., May 3, 1926.

1. Markwalder, Josif; and Starling, E. H.: J. Physiol. **47**:275, 1913-1914.
2. Drury, A. N., and Smith, F. M.: Heart **11**:71 (Jan.) 1924.
3. Cazamian: Bull. et mém. Soc. méd. d. hôp. de Paris **41**:46, 1917.
4. Leriche: Lyon chir. **16**:427, 1919.
5. Lewis, T., and Drury, A. N.: Heart **10**:301, 1923.

pressure, are similar. He suggested that the cardiac enlargement in these conditions was due to a deficient nutrition of the heart muscle resulting from the decrease in the mean arterial pressure. This conclusion was based on the study of the circulation of the limbs and he assumed that comparable changes occurred in the flow through the coronary arteries.

The object of this investigation was to determine the effects of specific changes in the systolic and the diastolic pressure on the coronary circulation.

METHOD

Dogs were employed in this series of experiments. These animals were prepared by a preliminary injection of morphine and a subsequent administration of chlorbutanol by stomach tube. Ether was used in sufficient amounts to complete the anesthesia. The blood pressure was recorded on the kymograph by a Straub membrane monometer. This instrument was employed in order to obtain a more accurate record of the systolic and the diastolic pressure. The chest was opened in the median line and a Morawitz-Zahn cannula [6] was introduced into the coronary sinus through the right auricular tip. The blood was prevented from coagulating by the use of heparin. The flow from the coronary sinus was allowed to escape into a 50 cc. graduate. These amounts were registered on the kymograph. The blood was maintained at body temperature and reintroduced into the femoral vein. Changes in the blood pressure were produced by constricting the thoracic aorta with an adjustable clamp and by the experimental production of arteriovenous aneurysm and aortic regurgitation. The arteriovenous aneurysm was produced by conducting the flow of the blood from a carotid artery through a small rubber bag to the jugular vein of the opposite side. The rubber bag was employed in order that the jugular vein might not be subjected to the full arterial pressure. The aortic regurgitation was produced by puncturing the aortic valves by means of a small wire introduced into the aorta through the carotid artery.

In those experiments in which the thoracic aorta was constricted by an adjustable clamp, it was possible, within certain limits, to increase the diastolic pressure without altering the systolic pressure. A typical experiment of this type is illustrated in figure 1. During the control period of this experiment the systolic pressure was 150 mm. of mercury and the diastolic 50. The rate of flow from the coronary sinus was 120 cc. per minute. After the aorta was constricted the diastolic pressure arose to 83 mm. of mercury and the systolic decreased to 145 and the flow from the coronary sinus increased to 187 cc. per minute. There was thus associated with the elevation of the diastolic pressure a striking

6. Morawitz and Zahn: Zentralbl. f. Physiol. **26**:465, 1912.

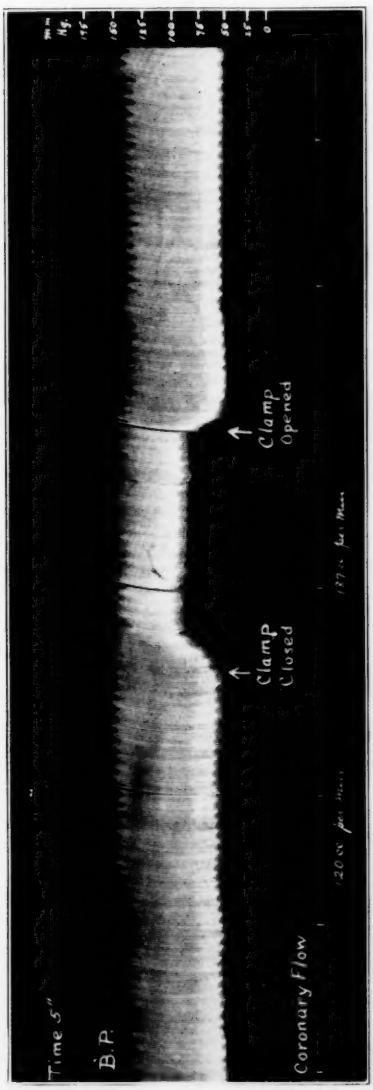

Fig. 1.—Effect of constricting the thoracic aorta with an adjustable clamp: diastolic pressure increased 66 per cent; coronary flow increased 56 per cent.

increase in the rate of coronary flow, even though the systolic pressure was slightly reduced. In all the experiments of this type the rate of coronary flow was increased and the percentage of increase was roughly proportional to the elevation of the diastolic pressure.

When the arteriovenous aneurysm was employed the diastolic pressure was reduced and the systolic increased. The alterations in the blood pressure and the associated changes in the coronary flow produced by this method are demonstrated by the experiment shown in figure 2. In this experiment, following the opening of the aneurysm, the systolic pressure increased from 155 to 165 mm. of mercury and the diastolic pressure fell from 72 to 57. The flow from the coronary sinus decreased from 180 to 157 cc. per minute. There was thus a 21 per cent reduction in the diastolic pressure and a 13 per cent decrease in the rate of coronary flow, even though there was an increase in the systolic pressure of 10 mm. In all the experiments of this group similar results were obtained.

In the experiments in which an aortic regurgitation was produced by puncturing the aortic valves, the results were similar to those of the arteriovenous aneurysm. The systolic pressure was increased, the diastolic decreased and there were corresponding changes in the coronary flow. The alterations in the blood pressure and the changes in the coronary flow varied with the extent to which the aortic valves were damaged. The results of one of these experiments is shown in figure 3. In the control period (fig. 3 *a*) the systolic pressure was 110 and the diastolic 50. The rate of flow from the coronary sinus was 240 cc. per minute. Following the puncture of one valve (fig. 3 *b*) the systolic pressure was increased to 120 and the diastolic fell to 30. The flow from the coronary sinus was reduced to 195 cc. per minute. Later the same valve cusp was torn loose from its base. Following this procedure (fig. 3 *c*) the systolic pressure at once increased to 150 and the diastolic fell to 15. The flow from the coronary sinus was further reduced to 150 cc. per minute. Even though the systolic pressure was increased 50 mm. of mercury over that of the control period, the rate of flow from the coronary sinus was decreased 90 cc. per minute. In other experiments of this nature comparable results were obtained.

CONCLUSIONS

The results of this series of experiments show that the rate of coronary flow is greatly altered by changes in the diastolic pressure, even in the presence of changes in the systolic pressure in the opposite direction. In one instance in which there was a reduction of only 5 mm. of mercury in the diastolic pressure associated with an increase of 10 in the systolic pressure, there was a decrease in the flow of the blood from the coronary sinus from 277 to 250 cc. per minute. Similarly in

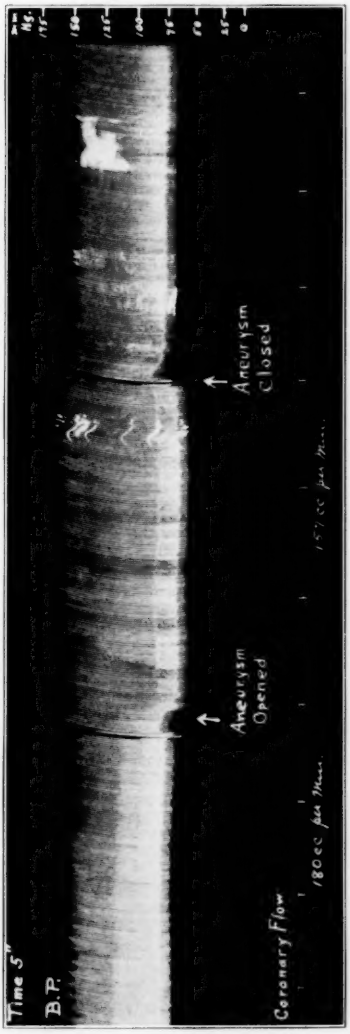

Fig. 2.—Effect of artificial arteriovenous aneurysm on coronary flow: diastolic pressure decreased 21 per cent; coronary flow decreased 13 per cent.

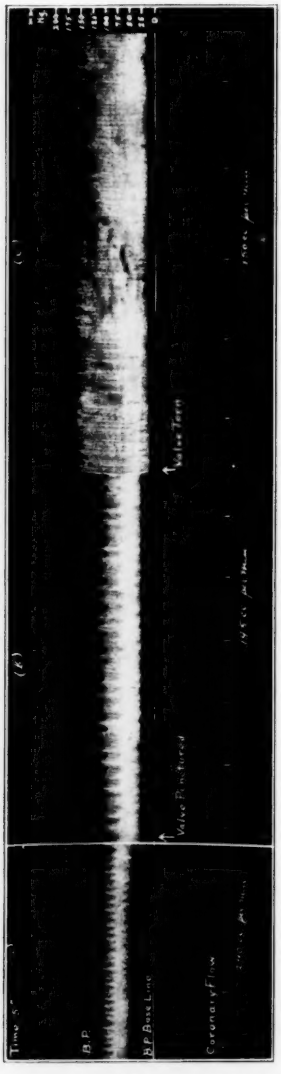

Fig. 3.—Effect of aortic regurgitation on coronary flow: *a*, control period; *b*, one valve cusp punctured: diastolic pressure decreased 40 per cent; coronary flow decreased 20 per cent; *c*, one valve torn loose: diastolic pressure decreased 70 per cent; coronary flow decreased 37 per cent.

those experiments in which there was a corresponding elevation of the diastolic pressure, even though the systolic pressure remained constant or was even slightly reduced, there was a comparable increase in the rate of coronary flow. It is evident from these results that the maintenance of an efficient coronary circulation is fundamentally dependent on the height of the diastolic pressure. It is not to be inferred, however, that the changes in the systolic pressure are entirely without influence on the rate of coronary flow. In experiments in which the diastolic pressure was reduced to a permanent low level, as in figure 3 *c* the rate of coronary flow may further be reduced by decreasing the systolic pressure and again increased by elevating the systolic blood pressure. In figure 3 *c*, however, even though the systolic pressure is 150, the flow from the coronary sinus is 90 cc. per minute less than during the control period (fig. 3 *a*). While the systolic phase of the blood pressure may, to a certain extent, influence the coronary flow, it is certainly subordinate to that of the diastolic pressure in maintaining the coronary circulation.

On the basis of these findings, it would seem that the decreased coronary flow associated with the diminished diastolic pressure in aortic regurgitation and arteriovenous aneurysm is probably a significant factor in the development of the cardiac hypertrophy and, later, cardiac failure.

AURICULAR FIBRILLATION WITH REGULAR VENTRICULAR RHYTHM AND RATE OVER SIXTY*

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The outstanding clinical feature of the cardiac arrhythmia now known to be associated with fibrillation of the auricles is irregularity of the ventricular beat. Before use of the electrocardiographic method made possible the recognition of the underlying disturbance in mechanism, the condition was termed pulsus irregularis perpetuus. The irregularity is not, however, invariably permanent. It may occur as paroxysms which terminate spontaneously; or a drug, such as quinidine, may be employed to restore sinus rhythm. It is also known that there may be complete heart block in auricular fibrillation, often the result of the therapeutic use of digitalis. As an accompaniment of A-V dissociation, regular idioventricular rhythm is established, usually at rates ranging from 30 to 40, though occasionally higher when the impulse is initiated in the junctional tissues.

More rarely it may be noted that, for varying periods, the ventricles, though beating at a rate of 60 or over, contract regularly. Such an event is of diagnostic importance in that it immediately presents the possibility that normal rhythm has spontaneously been resumed. Such was the opinion expressed in two of the cases shortly to be presented, until an electrocardiogram indicated that the auricles were still fibrillating. The occurrence of regular, rapid ventricular rhythm is worthy, as well, of theoretical consideration in relation to the analogy between fibrillation and flutter and their dependence on circus movement in the auricles.

During a three year period four cases were observed in which auricular fibrillation was associated with regular ventricular rhythm and rate over 60. In one of these patients (case 2) this change in rhythm occurred five times at intervals of a month or more; in another (case 4), in whom regularity was always interrupted by occasional interventricular intervals of unequal length, it was recorded three times in as many weeks. During the same three years, 227 patients with auricular fibrillation had records made in the cardiographic laboratory. According to these figures, the occurrence of regular ventricular rhythm with rate over 60 is uncommon in auricular fibrillation, having been recorded in less than 2 per cent of the cases.

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REPORT OF CASES

CASE 1.—J. S., a girl, aged 16 years, was admitted for the second time, Feb. 11, 1925, and died March 26. The diagnosis was cardiac hypertrophy; chronic cardiac valvular disease; mitral stenosis and insufficiency; aortic insufficiency; auricular fibrillation; cardiac insufficiency, and erysipelas.

There was history of diphtheria and scarlet fever in childhood and frequent attacks of tonsillitis. At 9, she had rheumatic fever, with a mild recrudescence at 12, for which she was admitted to the hospital in 1921, remaining six weeks.

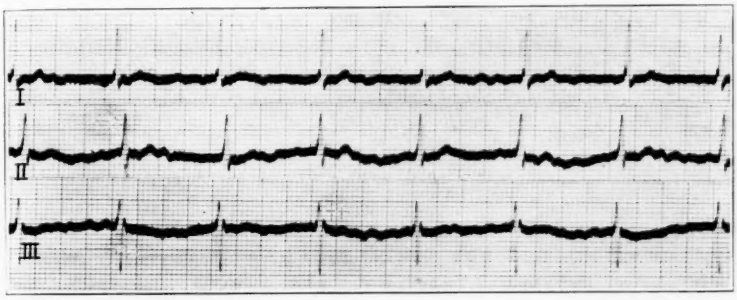

Fig. 1 (case 1).—Leads I, II and III, showing regular ventricular rhythm with rate of 74.

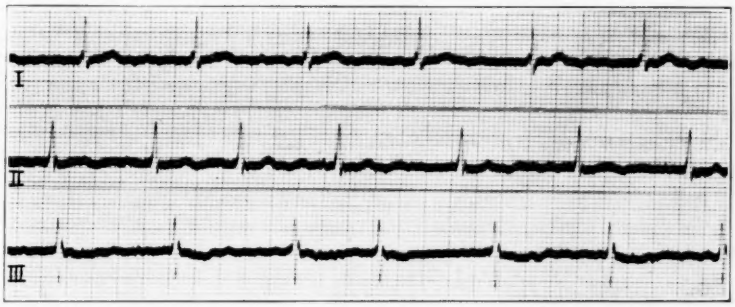

Fig. 2 (case 1).—Leads I, II and III, two days later than figure 1, showing regular ventricular rhythm with rate of 70 in Lead I, irregular rhythm in Leads II and III. It should be noted that there is no significant difference in the form of the complexes in the two sets of records.

Auricular fibrillation was first observed in November, 1923. There were progressive symptoms of cardiac failure, aggravated by frequent respiratory infections. Three days before death, erysipelas of the face appeared and hastened the end. Necropsy was not performed.

At the time of the final admission, February 11, there were signs of diffuse bilateral bronchitis, with probable patches of bronchopneumonia. The temperature was 102.8 but fell to a normal level in three days. Subsequently, there were irregular elevations to 102, interrupted by afebrile periods of several days. The heart was greatly enlarged. The rhythm was irregular; the apex rate 72, with small pulse deficit. The liver was swollen and there was moderate peripheral

edema. The white blood cells totaled 17,200, with 79 per cent polymorphonuclears; the red blood cells, 3,420,000, and hemoglobin, 60 per cent.

Prior to admission she had been taking two tablets of about 0.12 Gm. of digitalis daily for a number of weeks. During the first eight days in the hospital, she received 9 cc. of the tincture of digitalis, 2 cc. being given on the first day and 1 cc. daily thereafter, the drug having been omitted on the fourth day. At her own request, the digitalis in tablet form was then resumed, two tablets being given daily for ten days. During these nineteen days, the heart rate ranged from

TABLE 1.—Case 1.—*J. S., Aged 15*

Date, 1925	Electrocardiogram	Digitalis (Tincture)	Ventricular Rhythm	Ventricular Rate	T-Wave I	T-Wave II	T-Wave III	Remarks
March 9	7501	None for 6 days until March 8, when 2 cc. was given	Regular	74	+	+	—	Temperature, 101.4; bedside notes describe regularity of rhythm
March 10	7511	1 cc. March 9	Regular	72	+	+	—	Temperature, 101.2
March 11	7516	1 cc. March 10	Regular + Irregular	70	+	+	—	Temperature, 100.6
March 12	7525	None	Irregular	72	+	+	—	Temperature, 100

TABLE 2.—Case 1.—*Interventricular Intervals (Seconds)*

	Figure 1 Rate 74	Electrocardiogram 7511 Rate 72	Figure 2 Rate 70
	0.82	0.82	0.86
	0.81	0.78	0.77*
	0.81	0.81	0.88
	0.81	0.77	0.87
	0.82	0.83	0.88
	0.82	0.82	0.88
	0.81	0.80	0.88
	0.74	0.80	0.88
	0.78	0.80	0.84
	0.79	0.83	0.90
	0.75	0.83	0.90
	0.80	0.83	0.92
	0.80	0.83	0.90
	0.81	0.84	0.81
	0.81	0.82	0.66*
	0.79	0.82	0.77*
	0.80	0.84	0.96
	0.81	0.83	0.92
	0.79	0.82	0.88
	0.79	0.83	0.92
	0.81	0.85	0.65*
	0.81	0.83	0.90
	0.80	0.84	0.79*
	....	0.83	0.91
	....	0.83	0.92
	....	....	0.95
	....	....	0.66*
	....	....	0.90
	....	....	0.89
	....	....	0.88
	....	....	0.69*
	....	....	0.87
Maximum variation (seconds) exclusive of those marked with an asterisk (*).....	0.08	0.11	0.12

60 to 80, with little or no pulse deficit. No digitalis was given from March 2 to 7, inclusive. March 8, 2 cc. of tincture were given because of slight fever and elevation of heart rate to 100. The electrocardiogram, March 9, showed auricular fibrillation with regular ventricular rhythm and rate of 74 (table 1 and fig. 1). There was moderate left ventricular preponderance. The general form of the ventricular complexes resembled that of curves made several days previously when the rhythm was totally irregular and the rate 65. March 10 and 11, 1 cc. of tincture of digitalis was given. March 10, the rhythm was still perfectly regular;

March 11, portions of the record showed sequences of normal beats, while in places irregularity was noted (table 2). The rate was 80. March 12, the rhythm was again completely irregular, the rate being 72. The arrhythmia persisted with varying rates, until death fourteen days later. There were no form changes in the later graphic records.

CASE 2.—J. W., a boy, aged 13 years, admitted for the third time, July 3, 1922, and discharged improved, July 22, 1923, died in his sleep, Aug. 12, 1924. The diagnosis was chronic rheumatic fever; cardiac hypertrophy; chronic cardiac valvular disease; mitral stenosis and insufficiency; aortic insufficiency; auricular fibrillation, and cardiac insufficiency.

There was a history of indefinite joint pains and frequent sore throats. At the age of 7, a "leaky" heart was diagnosed by the school physician. At 11, symptoms of heart failure were first apparent and became more pronounced, with intervals of slight improvement, until death two years later. The occurrence of occasional fever and moderate leukocytosis was taken to indicate the persistence of an active, subacute rheumatic process in the heart. He was under continuous

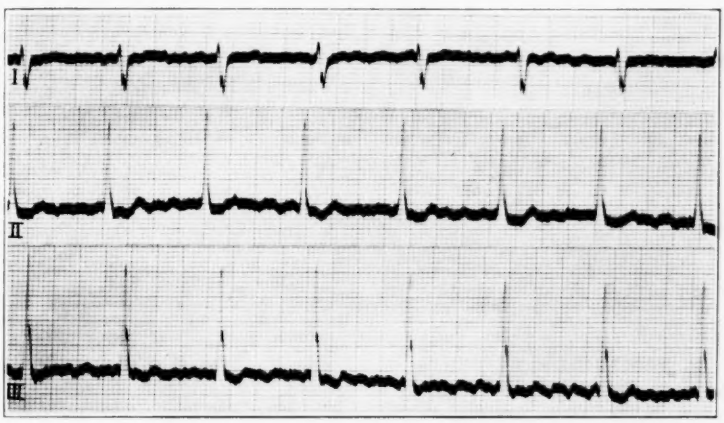

Fig. 3 (case 2).—Leads I, II and III, showing regular ventricular rhythm with rate of 78. In Leads II and III a 5 to 1 ratio is suggested between auricular (f) waves and the ventricular complexes. This would make the rate of the circus in the auricles 390 per minute.

observation in hospital and dispensary from July, 1920, to August, 1924. Fibrillation of the auricles was first noted July 3, 1922, and persisted to the end. No necropsy was performed.

Although more than fifty electrocardiograms were made, regular ventricular rhythm was observed on but six occasions (table 3). In one of these records, the regularity of the interventricular intervals was at times disturbed by shorter or longer pauses between beats (table 4).

CASE 3.—L. R., a boy, aged 11 years, admitted for the second time, May 26, 1925, was discharged, improved, August 13. The diagnosis was subacute rheumatic fever; cardiac hypertrophy; chronic cardiac valvular disease; mitral stenosis and insufficiency; adherent pericardium; auricular fibrillation, and cardiac insufficiency.

The boy was first admitted to the hospital, Dec. 22, 1924, complaining of shortness of breath and swelling of the abdomen. At 7, he had rheumatic fever. Dyspnea, which began at the time of the rheumatic attack, was so marked for two years that he was unable to attend school. In 1924, the heart was found to be enormously enlarged. While under observation and receiving digitalis, the

rhythm, which was regular on admission, changed first to auricular flutter, then to auricular fibrillation. The latter irregularity persisted during the time of subsequent observation.

On admission for the second time, there were signs of advanced heart failure. Orthopnea was extreme and there was general anasarca. He had been taking approximately 2 cc. of tincture of digitalis daily for a number of weeks, and this dosage was continued during the first two weeks of his hospital stay, during which the periods of regular ventricular rhythm were noted (tables 5 and 6). There were spikes of irregular fever, the temperature at times rising to 101.8. These febrile exacerbations were regarded as of rheumatic origin. It is worthy of note that at the time of regular ventricular rhythm one of the febrile episodes

TABLE 3.—Case 2.—*J. W., Aged 13*

Date, 1922	Electrocardiogram	Digitalis	Ventricular Rhythm	Ventricular Rate	T-Wave I	T-Wave II	T-Wave III	Remarks
July 29	3982	2 cc. of tincture daily for preceding 3 weeks	Regular	78	+	∓	∓	Temperature, 100; bedside note states, "cardiac rhythm is perfectly regular this morning"
September 7	4061	1.1 Gm. of digitan during preceding 4 days	Regular	76	+	∓	∓	Temperature, 100
September 8	4069	None	Regular + irregular	66-70	+	+	+	Temperature, 100.6; irregular rhythm had more rapid rate
October 25	4179	0.1-0.2 Gm. digitan once a day for preceding 2 weeks	Regular	71	+	∓	∓	Temperature, 102; pain in arm; nauseated
November 27	4268	0.1 Gm. digitan once a day for 10 days preceding	Regular	71	+	∓	∓	Temperature, 100.2; day before patient noticed that he felt "suddenly unusually comfortable"; the regular rhythm lasted about 36 hours; patient awoke during night of November 27 from a nightmare and was again aware of cardiac irregularity
December 29	4404	0.1-0.2 Gm. digitan once a day for 2 weeks preceding	Regular	74	∓	∓	∓	Temperature, 99.6; while playing cards, patient noticed that heart rhythm became regular; it remained so for 3 days

was taking place. The leukocytes at this time ranged from 12,000 to 17,000 and there was a moderate degree of anemia. There were at no time any evidences of digitalis intoxication.

Four months after leaving the hospital, the boy was alive but again having symptoms of advanced heart failure.

CASE 4.—M. M., a woman, aged 48, was admitted Aug. 15, 1924, and discharged, improved, December 20. The diagnosis was cardiac hypertrophy; chronic cardiac valvular disease; mitral stenosis and insufficiency; auricular fibrillation, and cardiac insufficiency.

No history of rheumatic fever was obtained, although the patient had frequent sore throats in childhood. For many years she noted palpitation on exertion or excitement. Dyspnea and weakness appeared three years before admission, night

sweats a year before, and there was edema of the legs for five months. For two years she had been taking digitalis in the form of digalen, the dosage being 10 drops three times a day.

From the time of admission, August 15, until October 14, varying amounts of digitalis were given (table 7) and numerous electrocardiograms were made. The curves all showed auricular fibrillation with moderate left ventricular preponderance. The rhythm was always irregular; the ventricular rate varied from

TABLE 4.—Case 2.—*Interventricular Intervals (Seconds)*

	Figure 3 Rate 78	Electrocardiogram 4061 Rate 76	Electrocardiogram 4069 Rate 70	Electrocardiogram 4179 Rate 71	Electrocardiogram 4268 Rate 71	Electrocardiogram 4404 Rate 74
	0.75	0.80	0.89	0.85	0.82	0.81
	0.75	0.80	0.88	0.84	0.83	0.81
	0.76	0.89	0.88	0.86	0.84	0.80
	0.77	0.89	0.87	0.87	0.83	0.80
	0.75	0.88	0.64*	0.84	0.83	0.80
	0.76	0.88	0.87	0.86	0.83	0.80
	0.75	0.86	0.88	0.87	0.82	0.81
	0.77	0.84	0.87	0.83	0.83	0.80
	0.76	0.85	0.88	0.86	0.82	0.80
	0.75	0.89	0.88	0.85	0.82	0.79
	0.78	0.89	0.88	0.87	0.83	0.81
	0.77	0.88	0.69*	0.87	0.84	0.80
	0.77	0.86	0.90	0.82	0.83	0.79
	0.77	0.89	0.89	0.85	0.84	0.79
	0.77	0.87	0.92	0.83	0.83	0.79
	0.75	0.85	0.90	0.87	0.84	0.81
	0.76	0.85	0.91	0.82	0.83	0.80
	0.75	0.86	0.90	0.80	0.83	0.79
	0.76	0.89	0.89	0.84	0.83	0.80
	0.74	0.88	0.88	0.82	0.83	0.80
	0.75	0.87	0.88	0.89	0.83	0.80
	0.75	0.89	0.85	0.89	0.83	0.79
	0.74	0.88	0.85	0.86	0.83	0.81
	0.75	0.89	0.81	0.86	0.83	0.79
	0.76	0.88	0.83	0.87	0.83	0.80
	0.75	0.88	0.83	0.87	0.83	0.79
	0.76	0.85	0.74*	0.82	0.83	0.81
	0.75	....	0.81	0.87	0.83	0.79
	0.75	.. .	0.83	0.89	0.82	0.79
	0.76	....	0.82	0.83	0.82	0.79
	0.76	....	0.81	0.87	0.83	0.79
	0.75	....	0.82	0.83	0.83	0.79
	...	....	0.87	0.82	0.83	0.79
	....	....	0.86	0.82	0.83	0.80
	....	....	0.83	0.86	0.83	0.80
	....	....	0.66*	0.83	0.82	0.79
	....	.. .	0.83	....	0.83	0.80
	...	....	....	....	0.81	0.79
	....	....	....	....	0.82	0.79
	....	....	....	....	....	0.80
	....	.. .	....	....	....	0.79
	....	....	....	....	....	0.81
	....	....	...	....	....	0.80
	....	....	....	....	....	0.81
Maximum variation (seconds) exclusive of those marked with an asterisk (*)	....	....	....	....	....	0.81
	....	....	....	....	....	0.81
	....	....	....	....	....	0.81
	....	....	....	....	....	0.81
	....	....	....	....	....	0.81
	....	....	....	....	....	0.81
	0.04	0.05	0.08	0.09	0.02	0.02

58 to 75. After having received from 1 cc. to 2 cc. of digitalis tincture daily for four weeks, a record, October 14, showed long sequences of regularly spaced ventricular complexes, occasionally interrupted by a few irregular shorter or longer interventricular intervals (table 8). A record made one week and again two weeks later showed similar periods of ventricular regularity. Subsequent electrocardiograms all showed irregular ventricular rhythm, with the rate ranging from 62 to 79. A daily dose of digitalis tincture, 1 cc., was given during the remainder of the patient's stay in the hospital. She was last seen in the

outpatient department, Nov. 19, 1925. At this time she was free of edema and able to walk a block or two without discomfort. She was taking digitalis tincture, 20 drops daily. An electrocardiogram showed auricular fibrillation with ventricular rate of 52, the rhythm of the ventricles being totally irregular.

COMMENT

A search of the literature has revealed but fifteen cases similar to the four here presented. Mackenzie,[1] with his customary clinical acumen, was the first to sense the unusual, which he described as follows:

> In a case recently under observation the rate under digitalis fell from 110 to 70 beats per minute. Prior to the administration of digitalis the rhythm was very irregular, but when the rate fell to 70 beats per minute it was quite regular. The patient had no jugular pulse, but by the electrocardiograph Lewis demonstrated that auricular fibrillation was present.

TABLE 5.—Case 3.—*L. R., Aged 11*

Date, 1925	Electrocardiogram	Digitalis (Tincture)	Ventricular Rhythm	Ventricular Rate	T-Wave I	T-Wave II	T-Wave III	Remarks
		2 cc. once a day for weeks	.....	..	..	..	..	Taking 2 cc. tincture digitalis daily for several weeks prior to admission on May 26
May 27-28	....	2 cc. once a day	.....	..	..	..	..	
May 29	7939	2 cc.	Irregular	80	+	—	—	
May 30-June 11	....	2 cc. once a day	.....	..	..	..	..	
June 12	8008	2 cc.	Regular	64	+	—	—	Temperature, 101.6; white blood cells, 17,200; bedside notes on this date state "for the last few days the heart has been regular"; marked anemia
June 13	8022	2 cc.	Regular + Irregular	60	+	—	—	Temperature, 100.4

In the group collected in table 8, age and sex apparently played no rôle as determining factors. In nine of the nineteen cases the heart lesions were considered to be rheumatic in origin; in one, syphilitic; seven were presumably due to degenerative processes incident to advancing years, and in two the etiology was not mentioned. All of my own patients had rheumatic mitral and aortic disease, enlarged and badly damaged hearts, and sufficient elevation of temperature to suggest that an active, acute or subacute rheumatic infection was present. The ventricular rates in the nineteen cases ranged from 56 to 90, the average being 68.6 per minute. Eight patients died within twenty months of the time of observation, six of these within three months. All suffered from advanced heart failure. The duration of regular rhythm, so far as was known, was from a few hours to a number of days. All of the

1. Mackenzie, J.: Auricular Fibrillation, Brit. M. J. **2**:872 (Oct. 14) 1911.

patients were receiving digitalis, a majority of them in full therapeutic doses.

Two possible explanations of the mechanism naturally suggest themselves. The first assumes complete auriculoventricular dissociation, the regular beating of the ventricles being initiated by a pacemaker situated at or in the vicinity of the A-V node. The fact that all the patients received digitalis lends some weight to the concept that heart block was present. As pointed out by Lewis,[2] the intrinsic ventricular rhythm is especially fast when heart block has been induced by digitalis. In his

TABLE 6.—Case 3.—*Interventricular Intervals (Seconds)*

	Electrocardiogram 8008 Rate 64	Electrocardiogram 8022 Rate 60
	0.90	1.00*
	0.91	0.99
	0.91	0.97
	0.89	0.98
	0.90	0.98
	0.90	0.99
	0.92	0.96
	0.91	0.97
	0.91	0.99
	0.91	0.96
	0.90	0.95
	0.92	0.96
	0.92	0.98
	0.88	0.96
	0.90	0.97
	0.90	1.00*
	0.90	1.00*
	0.89	0.95
	0.90	0.96
Maximum variation	0.90	....
(seconds) exclusive	0.91	....
of those marked	———	———
with an asterisk (*)	0.04	0.04

opinion this condition was present in his own case, of which the electrocardiogram is reproduced in a recent issue of his book.[3]

An analogous series of twelve cases of complete A-V dissociation, with the auricles contracting normally and with ventricular rates in excess of 60, has been compiled by Hewlett.[4] A majority of these also were ascribed to the depression of A-V conduction by digitalis. In all, the disturbance was transient or intermittent.

2. Lewis, T.: Observations Upon Disorders of the Heart's Action, Heart **3**:282, 1911-1912.

3. Lewis, T.: Clinical Electrocardiography, Ed. 3, Shaw and Sons, 1924, p. 95.

4. Hewlett, A. W.: A Case Showing Rapid Ventricular Ryhthm with Periods of Auriculoventricular Dissociation, Heart **10**:9 (April) 1923.

TABLE 7.—Case 4.—*M. M., Aged 48*

Date, 1924	Electrocardiogram	Digitalis	Ventricular Rhythm	Ventricular Rate	T-Wave I	T-Wave II	T-Wave III	Remarks
September 18 to October 6	....	Tincture of digitalis, 1-2 cc. once a day	.....	.....	..	..	..	
October 7	6883	.....	Irregular	62-64	—	∓	+	
October 8 to 14	....	Tincture of digitalis, 1-2 cc. once a day	.....	.....	..	..	..	
October 14	6894	2 cc.	Regular + irregular	72-76	—	+	+	Quite comfortable; no fever; little or no pulse deficit; slight variations in length of cycles in parts of records; during periods of regular ventricular rhythm, rate varies from 72 to 76
October 14 to 19	....	1-2 cc. once a day	.....	.....	..	..	..	
October 20	....	4 cc	.....	.....	..	..	..	
October 21	6921	.....	Regular + irregular	48-74	—	+	+	Temperature, 99.6; vomited later in the day; in lead I is shown transition from slower, irregular rhythm to more rapid, regular one; slow rate, 48
October 22 to 25	....	1 cc. once a day	.....	.....	..	..	..	
October 25 to 27	....	None	.....	.....	..	..	..	
October 28	6949	.....	Regular + irregular	60-70	..	..	..	Temperature, 100.6; for relatively long periods, there was a series of regular sequences, interrupted by occasional irregularity in ventricular rhythm; the irregular was the slower rhythm, as in previous record

TABLE 8.—Case 4.—*Interventricular Intervals (Seconds)*

	Electrocardiogram 6894 Rate 72-76	Electrocardiogram 6921 Rate 48-74	Electrocardiogram 6949 Rate 60-70
	0.80	1.47*	0.85
	0.81	0.91*	0.89
	0.80	1.30*	0.85
	0.89	0.79	0.89
	0.70*	0.78	0.87
	0.70*	0.78	0.87
	0.69*	0.78	0.86
	0.81	0.79	0.87
	0.83	0.81	0.87
	0.83	0.81	0.87
	0.83	0.81	0.87
	0.82	0.81	1.28*
	0.83	0.79	1.17*
	0.82	0.79	0.86
	0.82	0.79	0.83
	0.81	0.79	0.84
	0.80	0.79	0.83
	0.84	0.81	0.82
	0.76*	0.79	0.82
	0.97*	0.80	0.83
	0.83	0.79	0.86
	0.79	0.80	0.86
	0.86	0.80	0.85
	0.85	0.80	0.85
	0.82	....	0.85
	0.83	....	0.81
	0.82	....	0.76*
	0.85	....	0.92*
	0.81	.. .	....
	0.80	....	....
Maximum variation (seconds) exclusive of those marked with an asterisk (*).....	0.80 —0.91	.. . .	....
	0.07	0.02	0.07

TABLE 9.—*Summary of Reported Cases of Auricular Fibrillation with Regular Ventricular Rhythm and Rate Over 55*

Author	Age	Sex*	Etiology	Clinical Diagnosis	Total Digitalis Given	Ventricular Rate	Remarks
Mackenzie [1]	..	..	.....	.....	Full doses	70	Electrocardiogram by Thomas Lewis (not published)
Lewis [2]	17	♀	Rheumatism	Mitral stenosis and insufficiency	For 7 days, 40 minims of tincture daily; for one day, 9 minims	80-90	Died on the sixth day after onset of regular rhythm
Lea †	78	♂	.....	.....	Full doses	75	
Dock and Levine [6]	32	♂	Rheumatism	Mitral stenosis and insufficiency	1.2 Gm. in 2 days	57-73-73	Three observations; after 1.2 Gm. was given, regular rhythm apparently persisted for 4 days; improved
	52	♂	.....	Chronic myocarditis; chronic nephritis; hypertension	5.5 Gm in 65 days	81	Died in 92 days
	72	♂	.....	Chronic myocarditis	2.65 Gm. in 10 days	60	Died in 10 months
	65	♂	.....	Chronic myocarditis; hypertension	Tincture; to the point of nausea	85	Improved
	40	♀	Rheumatism	Mitral stenosis and insufficiency	1.7 Gm. in 7 days	66	Died in 2 months
	48	♀	Rheumatism	Aortic stenosis	Digalen, 5 drops, twice a day for 2 months	58	Improved
	52	♂	.....	Chronic myocarditis	2.5 Gm. in 6 days	88	Improved
	57	♂	.....	Chronic myocarditis	2.1 Gm. in 3 days	56	Died in 14 days
	30	♀	Rheumatism	Mitral stenosis and insufficiency	1.3 Gm. in 7 days	68	Died in 21 days
	50	♂	.....	Chronic myocarditis; aortic insufficiency	2.1 Gm. in 7 days	75	Two observations; improved
					2.9 Gm. in 21 days	75	
	57	♂	Syphilis	Syphilitic aortitis; aortic insufficiency	3.0 Gm. in 7 days	58	Improved
	54	♀	.....	Chronic myocarditis	3.85 Gm. in 22 days	59	Two observations; improved
					4.45 Gm. in 28 days	58	
Levy	16	♀	Rheumatism	Mitral stenosis and insufficiency; aortic insufficiency	None for 6 days until day preceding, when 2 cc. of tincture was given	74	Three observations
					3 cc. in 2 days	72	
					4 cc. in 3 days	70	Died 2 weeks later
	13	♂	Rheumatism	Mitral stenosis and insufficiency; aortic insufficiency	2 cc. daily for 3 weeks	78	Six observations
					1.1 Gm. during 4 days	76	
					1.1 Gm. during 5 days	66-70	Rhythm irregular for short periods
					0.1-0.2 Gm. once a day for 2 weeks	71	
					0.1 Gm. once a day for 10 days	71	
					0.1-0.2 Gm. once a day for 2 weeks	74	Died 20 months later
	48	♀	Rheumatism	Mitral stenosis and insufficiency	1-2 cc. of tincture once a day for 4 weeks	72-76	Three observations; always short periods of irregular rhythm; improved
					1-2 cc. once a day for 5 weeks	74	
					None for 4 days; before that 1 cc. once a day for 1 week	70	Further improvement when seen 1 year later
	11	♂	Rheumatism	Mitral stenosis and insufficiency; adherent pericardium	2 cc. once a day for 2 weeks	64	Two observations; improved
					2 cc. once a day for 2 weeks	60	Four months later, alive but failing

* In this table, ♂ indicates male; ♀, female.
† Lea, E.: Lancet **1**: 1289, 1915. Other authors are referred to in text.

Another interpretation of the regularity of the ventricular contractions in fibrillation is possible in the light of the demonstration that auricular fibrillation, like flutter, is dependent on a circulating wave in the auricles.[5] In fact, fibrillation may be regarded as a variety of flutter, differing from the latter in that the path pursued by the circus is inconstant, its rate of travel is more rapid and the separate circuits are completed in varying times. Although in fibrillation coordinate contraction is no longer carried on by the auricles, the ventricles respond to occasional impulses derived from the circulating waves in the auricles. The conditions that determine the frequency and degree of regularity of ventricular contractions are not fully understood. The rate and path of the circus, the conductivity of the A-V junctional tissues and their state of refractoriness are probable factors concerned.

In flutter it is believed that the ventricular response is determined largely by the existing grade of A-V block. Thus, there are commonly from 2 to 5 auricular contractions to each ventricular beat, the rhythm of the ventricles being at times regular, at other times irregular. Is it not possible that in these cases of fibrillation with regular ventricular rhythm at rates more rapid than are commonly observed in A-V dissociation a condition exists which is analogous to that observed in flutter and that we are dealing with a partial block which, during the periods of ventricular regularity, is constant and at other times varies? The question has, indeed, been raised [6] and some evidence may be adduced in favor of this view.

The amounts of digitalis given in the four cases reported in this article are not usually regarded as sufficient to induce complete heart block. Nor do the T waves in the electrocardiograms show changes indicative of full digitalis effect (tables 1, 3, 5 and 7). In several instances, although digitalis therapy was continued after the onset of regular ventricular rhythm, irregularity recurred within a day or two. On other occasions, similar or larger doses were given to all of these patients without resultant ventricular regularity. The first patient is worthy of special mention in this connection. For ten days she had received 0.12 Gm. of digitalis daily; then none for six days; then 2 cc. of tincture for one day. The following morning the ventricular rhythm was regular, the rate 74. In spite of the administration of 1 cc. of tincture daily for the next two days, a combination of regular and

5. Lewis, T.: The Nature of Auricular Fibrillation as It Occurs in Patients, Heart **8**:193 (May) 1921.

6. Dock, W., and Levine, S. A.: The Occurrence of Regular Ventricular Rhythm with a Rate of Over Fifty Cases of Auricular Fibrillation, Am. J. M. Sc. **167**:664 (May) 1924.

irregular rhythm was followed on the second day by total arrhythmia. It is interesting but unprofitable to speculate as to the possible effect of active rheumatic lesions on the susceptibility of the junctional tissues.

It is striking that there is no significant variation in the form of the ventricular complexes of the electrocardiograms during periods of regular and irregular rhythm (fig. 1). They appear, in fact, to be essentially identical in all of the cases. Such constancy of form points to the uninterrupted supraventricular origin of the impulses giving rise to these complexes and argues against their initiation in the junctional or ventricular tissues during the periods of ventricular regularity.

Complete heart block due to digitalis, once established, ordinarily persists without variation until the action of the drug has worn off. It does not exhibit fluctuations in interventricular intervals, as is evident in some of the curves, measurements of which are given in tables 6 and 8. Case 4 (table 8) is a striking example of the combination of regular and irregular ventricular rhythm, long sequences of absolute regularity being broken by occasional longer interventricular intervals. It suggests partial rather than complete block. In two of the other patients similar combined rhythms were recorded. It is of interest that the irregular rhythm may have either the faster (case 2) or the slower rate (case 4).

A satisfactory demonstration of an absolute ratio between the number of auricular cycles and ventricular beats has not been possible. In leads II and III, figure 2, a 5 to 1 ratio is suggested. This would make the rate of the circus 390 per minute. Curves made with chest leads in case 3 were likewise not conclusive. Atropine tests and vagus or ocular pressure experiments were not done. When tried in several of their cases by Dock and Levine, negative results were obtained in that no change in ventricular rate was observed. In their patients vagus effects apparently did not play a part in controlling the mechanism. Such tests would not necessarily decide the issue with finality since, as Hewlett has emphasized, rhythms arising in the A-V node are very susceptible to vagus influences. Change in ventricular rate following vagal inhibition or stimulation might result whether complete block was or was not present.

Final proof as to the nature of the mechanism has not been brought. The possible analogy to conditions prevailing in flutter is of interest. It is not unlikely that this disorder in rhythm, being transient, occurs more frequently than is commonly recognized.

SUMMARY

1. Four cases of auricular fibrillation have been reported in which the ventricular rhythm showed periods of regularity, the rate of the ventricles being over 60 per minute. Fifteen similar cases have been found in the literature, in which the ventricular rate was over 55.

2. The regular ventricular rhythm lasted from a few hours to several days.

3. The condition is of diagnostic import in that it may simulate normal (sinus) rhythm.

4. The nature of the underlying mechanism has been discussed. Evidence may be adduced in support of the existence of either complete or partial A-V block. The possible analogy to partial block as it occurs in auricular flutter has been pointed out. Final proof of either hypothesis is lacking.

EXTERNAL FACTORS CAUSING VARIABLE RESULTS IN THE KOTTMANN REACTION *

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Kottmann [1] in 1920 demonstrated a reaction in human blood serum which he asserted varied with the activity of the thyroid. The increased or decreased function of the gland was assumed to affect the protective colloidal properties of the blood serum of the patient, and this property, in turn, to affect a certain photochemic reaction of the serum. By means of this, according to his hypothesis, the thyroid activity could be measured.

The technic of the Kottmann reaction is essentially as follows: To 1 cc. of fresh unhemolyzed serum in a small Wassermann type test tube, 0.25 cc. of 0.5 per cent potassium iodide is added, then 0.3 cc. of 0.5 per cent silver nitrate, and the tube shaken after each addition to insure uniform mixing. The tube is then exposed to a 500 watt mazda lamp at a distance of 25 cm. for five minutes, at the end of which, 0.5 cc. of 0.25 per cent hydroquinone is added with shaking. The color changes are carefully noted at definite time intervals thereafter. In our work we have considered as a delayed reaction one in which no color change could be observed ten minutes after the addition of hydroquinone.

Kottmann's theory of the cause of the differing speeds with which this color development takes place, with different serums, is this: The sensitivity of silver iodide particles to light is proportional to their size; the more finely dispersed their state, the less photosensitive they are, while the coarser the particles, the more sensitive they are. A high protective colloid content or power in the serum, then, might keep the silver iodide in a fine state of dispersion, lessen its photosensitivity, and delay color appearance on the addition of the developer, hydroquinone. A low protective colloid content might conversely allow the formation of coarser particles, with a greater photosensitivity, and so result in a much quicker development of color.

Kottmann found that the serum of a hyperthyroid patient gave a delayed development of color, while a hypothyroid case gave an accelerated reaction, as compared with his group of normal controls.

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* From the laboratory of internal medicine in the Boston Psychopathic Hospital.

1. Kottmann, K.: Kolloidchemische Untersuchungen über Schildrusenprobleme, Schweiz. med. Wchnschr. **50**:644 (July 22) 1920.

Petersen, H'Doubler and Levinson [2] in 1922 agreed with Kottmann, finding a delayed reaction in sixty-five out of seventy hyperthyroid cases, and a normal reaction in all but three of 139 normals.

Raphael [3] worked on psychotic patients without thyroid complication, and found a most remarkable parallel between the affective disorders of a large group of subjects and their Kottmann reactions. He carried out tests at intervals on the same patient during his clinical improvement or progress and obtained a striking agreement between the patient's condition and the Kottmann reaction, in all but eight out of 754 observations on 291 patients.

Saunders [4] reports 400 Kottmann reactions done on psychotic patients, 105 of which show a "delayed" reaction, the time of which he did not give. Of these only one showed any clinical symptoms of hyperthyroidism, while "most of the others had very indefinite symptoms."

Kramer,[5] using the reaction as an index of thyroid function, obtained unsatisfactory results, getting a retardation of over fifteen minutes in only one out of fourteen cases of hyperthyroidism. In his technic, however, it should be noted that his time for exposure to light is given as fifteen minutes with a 500 candlepower lamp, rather than the five minutes with a 500 watt lamp specified by Kottmann.

In our own work we were interested in the possible relation of the Kottmann reaction to the affective states of psychotic patients, as Kottmann and Petersen had observed that fright or excitement in a patient tended to delay the reaction. Single observations were made on seventy patients without thyroid complication according to the technic set forth above. We found that of twenty-three delayed reactions, eleven were from disturbed and excited patients, six from depressed, and six from quiet and cooperative patients. Of forty-seven cases within normal limits or accelerated, there were eleven excited, six depressed and thirty quiet and cooperative patients. From this it may be seen that while the percentage of excited patients is highest in the group showing delayed reactions and of normal patients is highest in the group showing so-called normal reactions, there is no striking consistency, which would show that a delayed reaction is indicative of an emotional state.

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2. Petersen, W. F.; H'Doubler, F. T., and Levinson, S. A.: The Kottmann Reaction for Thyroid Activity, J. A. M. A. **78**:1022 (April 8) 1922.

3. Raphael, Theophile; and Smith, G. J.: The Kottmann Reaction as Applied to Psychiatric Cases, Am. J. Psychiat. **4**:161 (Oct.) 1924.

4. Saunders, A. M.: The Kottmann Reaction in the Insane, J. Lab. & Clin. Med. **9**:401 (March) 1924.

5. Kramer, D. W.: The Kottmann Reaction in Thyroid Dysfunction, Am. J. M. Sc. **170**:75 (July) 1925.

We were able to obtain only three definitely hyperthyroid cases, an exophthalmic goiter case with a basal metabolism of plus 95 per cent, a thyrocardiac case with a basal metabolic rate of plus 54 per cent and a case of toxic colloid adenoma of the thyroid. All three showed a normal reaction with beginning color change within five minutes. These cases were obtained through the courtesy of the surgical service of the New England Deaconess Hospital.

We then decided to investigate the technic of the reaction before continuing further with its clinical application. Morse and Fitch [6] had already stated that preservation of the blood serum tended to accelerate the Kottmann reaction, and this we also found to be true. One of our serums, giving a reaction in which the first color change occurred at the end of fifteen minutes, gave a reaction five hours later in which the first color change was observed at the end of seven minutes. Another serum giving a delayed reaction of one hour gave a reaction within a minute twenty-four hours later. Both serums had stood at room temperature. In addition to this we observed, as did Morse and Fitch, that the first color development began definitely at the surface of the serum.

Morse and Fitch believed that this accelerated action was due, at least in part, to a loss of carbon dioxide from the blood serum. In their experimental evidence, they reported a serum giving a delayed reaction, which when aerated for fifteen minutes gave an accelerated reaction, and which, resaturated with alveolar air, gave the original delayed reaction, with identical times for changes in color. They found also that the acceleration of the reaction was directly proportional to the duration of the aeration of the serum.

With the purpose of investigating further this carbon dioxide factor in the Kottmann reaction, we carried out controlled experiments as follows:

1. To confirm the aeration experiments of Morse and Fitch, 1 cc. of serum was perfused with air and 1 cc. with pure oxygen.

2. To study the effect of increased concentration of carbon dioxide, 1 cc. of serum was perfused with carbon dioxide.

3. To study the effect of increased temperature, 1 cc. of serum was heated for a short time in a water bath.

The technic of the experiments was as follows: A sufficient amount of fasting blood was centrifugalized as soon as clotted, and 1 cc. of serum added to each of five tubes. A drop of caprylic alcohol was added to each of the five tubes to prevent foaming in the case of those to be

6. Morse, Sterne; and Fitch, C. M.: The Kottmann Reaction for Thyroid Activity: Carbon Dioxide in the Tested Serum, J. Lab. & Clin. Med. **8**:692 (July) 1923.

perfused with gas. Each perfusion was timed and limited to one minute, the speed of perfusion being regulated so far as possible. Carbon dioxide was generated from calcium carbonate and dilute hydrochloric acid in a medium sized Erlenmeyer flask. The oxygen was obtained from a tank used for medical work, and the air from a suction blower pump. When the temperature factor was being studied, the serums were heated in a water bath at 45-46 C. for three minutes, while the control stood at room temperature. All tubes were then treated according to the standard technic, the gradations in color being read at the end of five and ten minutes after the addition of hydroquinone. The following method of notation was adopted:

0 no color change
⊕ doubtful
+ faint
++ light brown
+++ brown (reddish)
++++ dark brown (chocolate)

From table 1, it may be seen that air and oxygen perfusion for one minute tend to accelerate the reaction, and that the latter is apparently more effective. To obtain significant conclusions, however, as to the relative effects of air and pure oxygen on this reaction longer perfusion is necessary.

TABLE 1.—*Effect of Perfusion of Serums with Oxygen, Air and Carbon Dioxide and of Heating Serums on Kottmann Reaction* *

Experiment	Control	Oxygen	Air	Carbon Dioxide	Heat
1	0	++	++	0	0
2	0	+++	++	0	+
3	++	++	++	0	++
4	0	++	+	0	+
5	+	+++	+	+	+++
6	++	++	+++	0	+
7	+	++	++	0	+
8	++	+++	++	0	++++
9	++	+++	+	0	++
10	++	+++	++⊕	0	+++
11	++	+++	—	0	+++
12	++	+++	+++	—	+++
13	++	++++	+++	0	++

* Readings were taken at the end of ten minutes after the addition of hydroquinone.

The effect of carbon dioxide introduced into the serum is a striking and almost entirely consistent retardation of the color development. In every case but one, the serum gives a distinctly delayed reaction as compared with its control. Although no definite time record was kept after ten minutes, most of the carbon dioxide treated serums were observed to show a slight and gradual change in color only after an hour or longer; the controls showed a color change long before, in every case but case 5. In a series of six similar experiments previously performed, we found a delayed reaction in every case.

The effect of heating in a water bath for three minutes at 45-46 C. in eight cases out of thirteen was a definite acceleration. Since at the increased temperature there would be a loss of carbon dioxide from the serum, this result is the expected one as compared with the delayed reactions obtained after carbon dioxide perfusion. The experiments provide partial confirmation of the suggestion of Morse and Fitch, that carbon dioxide content of the serum or, in other words, the hydrogen ion concentration is an important variable in the Kottmann technic.

We decided to investigate the temperature factor further, lengthening the time of heating. The technic was as follows: A copper water bath large enough to be kept at a temperature between 45 and 46 C. for fifteen minutes without difficulty was used. Into the accessory tube rack, tubes containing 1 cc. of serum each (obtained in the same manner as before) were placed, and eight minutes later, more tubes, and five minutes later, the last tubes. Three minutes later all tubes were taken out simultaneously, and treated according to the standard technic. We found it most convenient to work with no more than two sets of serums at one time, more than that making accuracy in reading impracticable.

TABLE 2.—*Effect of Heating Serums at 45-46 C. for Three, Seven and Fifteen Minutes, Respectively* *

Experiment	Control (No Heating)	Heating 3 Minutes	7 Minutes	15 Minutes
1	+	++	++⊕	+++
2	⊕	+++	++	++++
3	+	+++⊕	+++⊕	++++
4	+	++	++⊕	++++
5	+	++	+⊕	+++
6	+	++	++⊕	+++⊕
7	+	+⊕	+⊕	++
8	+	+⊕	++⊕	—

* Readings were taken five minutes after the addition of hydroquinone.

From table 2 it may be seen that the reaction is consistently accelerated on heating, and that the acceleration is marked after fifteen minutes heating. For lesser periods of heating, however, the acceleration does not always proceed in direct proportion to the length of time of heating the serum. In four of the seven minute serums there is a greater acceleration as compared with the corresponding three minute serums, but in two there is no greater acceleration, and in two there is an actual retardation as compared with the three minute serums, though not with the control. This variability is unmistakable, and we have no explanation to offer except that if the protective colloid power, so called, of the serum is the determining factor in the photosensitivity of the Kottmann serum mixture, and if on heating the serum gradually under-

goes a loss of carbon dioxide with a decreasing hydrogen ion concentration, there may be one or more optimal p_H values in the serum at which this colloid phenomenon takes place.

Petersen [7] states that he found that dog serum that had been for several days in the refrigerator lost its protective power to a "considerable extent," and differed in this respect from serums obtained from patients with hyperthyroidism; these he kept for several weeks with "only a partial loss" of their protective property. We found a definite acceleration in five serums that were allowed to stand for twenty-four hours, at room temperature. In a few experiments in which Kottmann reactions were done on samples of the same serum that had stood at room temperature (table 3) at two hour intervals, we found a general tendency toward an acceleration of the reaction with increased time of exposure to air, but here again as with the heating experiment, a curious inconsistency in the direct proportion of acceleration to time.

TABLE 3.—*Effect of Exposure of Serums at Room Temperature for Definite Periods of Time* *

Experiment	Immediately	2 Hours	4 Hours	6 Hours	8 Hours	24 Hours
1.....	++	+++	+++⊕	+++	—	+++
2.....	⊕	++	++	+	—	++++
3.....	++	0	++⊕	⊕	—	++++
4.....	+	+	++	+⊕	—	—
5.....	0	+	0	0	—	—
6.....	++	++	+++	+++⊕	+++⊕	..

* Readings were taken at the end of five minutes after the addition of hydroquinone.

From the foregoing experiments, however, we feel certain that the p_H of the blood serum is a most important, if not the predominating, factor in the reaction. This factor is so easily varied that the necessary handling of the serums introduces an uncontrollable variable unless the laboratory is elaborately equipped for the purpose. The consistent results obtained by Kottmann, Petersen and Raphael in the differentiation of hyperthyroid cases from normal can only be explained by a control over these variables by a technic that they fail to record in their articles. If hyperthyroidism caused an indefinite delay in color change, as compared with the normal, this p_H factor caused by standing at room temperature and manipulation of the serum would admittedly be of minor significance. The delay in the cases reported by other investigators, if defined at all, has not been long enough to discount, in our opinion, the effects of the p_H variable. Consequently, we believe that the test does not admit of sufficiently accurate reading to be of practical use in the clinical laboratory.

7. Petersen, W. F.; H'Doubler, F. T.; Levinson, S. A., and Laibe, J. E. F.: Studies in the Kottmann Reaction for Thyroid Activity, Arch. Int. Med. **30**:386 (Sept.) 1922.

SUMMARY

1. The Kottmann reaction was performed on serums from seventy psychotic patients and three patients with hyperthyroidism.

2. No correlation between the emotional state and the Kottmann reaction was demonstrable.

3. In the hyperthyroid cases a normal rather than a delayed reaction was obtained.

4. A series of experiments investigating the technic of the Kottmann reaction, especially from the standpoint of carbon dioxide content of the serum, was performed.

5. Perfusion of serum with carbon dioxide for one minute causes a striking and consistent retardation of the Kottmann reaction.

6. Heating of the serum for fifteen minutes at 45 C. causes a striking and consistent acceleration of the reaction.

7. Exposure of the serum to room temperature for any length of time causes in general an acceleration of the reaction; exposure for twenty-four hours a striking acceleration.

8. The foregoing procedure is equivalent to increasing and decreasing the carbon dioxide content of the serum and consequently varying the hydrogen ion concentration.

9. These experiments demonstrate an uncontrollable variable inherent in the technic described by Kottmann and subsequent workers.

10. Since the distinction between a normal and a delayed reaction, as reported by various observers up to this time, is not striking or clearly defined, and since we have shown that the p_H variation of the blood serum as manipulated in the reaction is inevitable and sufficient to interfere with conclusions drawn from the reaction, we believe that the Kottmann reaction is of no diagnostic or prognostic significance in the clinical laboratory.

WATER METABOLISM

IV. SUGAR METABOLISM IN DEHYDRATION *

EDMUND ANDREWS, M.D.
CHICAGO

The effect on metabolism of varying degrees of hydration has received but little attention. Our metabolic laws have been assumed to apply rigidly and quantitatively, whether the body was supercharged with water or dehydrated to the point of anuria. Such an assumption is theoretically unsound. One would not expect chemical changes to occur with the same results, either quantitatively or qualitatively in solutions of different strengths. Hitherto, investigators have assumed that this was the case and water metabolism has only been studied in relation to edema, acidosis, nephritis, fevers and the general theory of flushing out or diluting toxins. The following experiments show that the problem is deeper and the varying concentration of the tissue fluids produces profound changes in what have previously been regarded as independent metabolic phenomena.

The injection of equivalent amounts of insulin into animals has been expected to bring about a fall in the blood sugar of about the same depth and duration. The following curves will serve as controls for such experiments. Each dog received one half unit of insulin per kilogram of body weight. It will be noted that after a slight transient rise of 5-10 mg., a fall of 10-15 mg. occurs and at the end of about two and one half hours a return to normal has taken place (chart 1).

In order to test the effect on this insulin curve of dehydration dogs were injected with 10 cc. per kilogram of 5 per cent sodium chloride intravenously the day before the experiments. These animals under such stimulus passed about 500 cc. more urine than normal and lost 0.5 Kg. in weight. The concentration of the blood as measured by the refractometer was increased markedly. The fall was quite constant, being about 5-6 degrees in the refractometric index. This loss of fluid is not enough to produce any clinical changes. The dogs showed no evidences of illness and were up and playing about the pen. Temperature changes were not observed during the injections but the temperature was normal when the experiments were made. In other words the degree of dehydration thus brought about was strictly within the limits of ordinary clinical variation. Such animals when injected with equivalent amounts of insulin show a very different reaction. The initial rise in the blood sugar, which is quite constant in the controls,

* From the Surgical Department, University of Illinois College of Medicine.

is less or absent entirely. The fall is much more pronounced, averaging about twice as much as in the controls (20 in normals, 40 in dehydrated animals) and the most striking phenomenon in the length of the curve. Thus far in the work none of the animals have been followed for more than eight hours but at the end of that time there is no sign of a return to normal levels (chart 2).

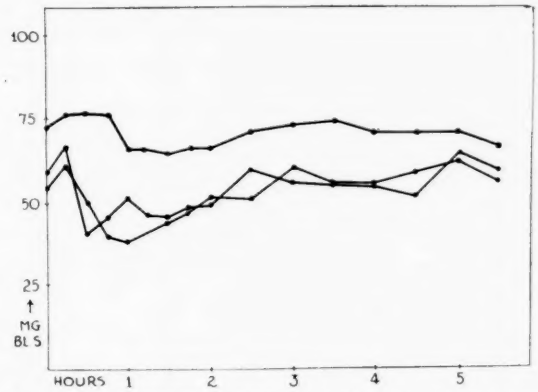

Chart 1.—Control insulin curve (one-half unit of insulin per kilogram).

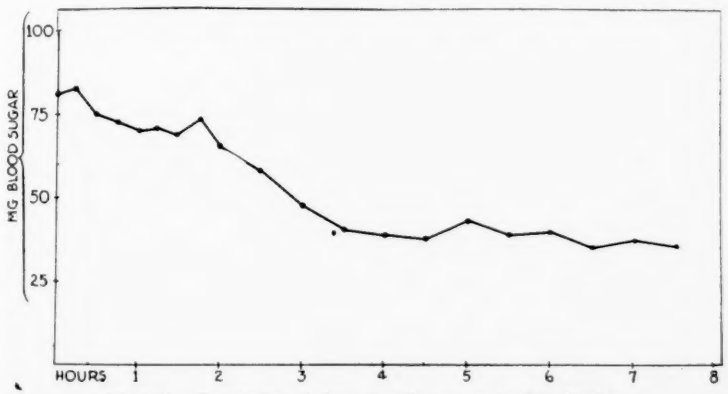

Chart 2.—Composite of three insulin curves in dehydration.

The question arose at once, "Was it the salt solution which produced these changes?" Therefore the experiments were repeated on animals who were dehydrated by the deprivation of water for forty-eight hours and it is evident from chart 3 that dehydration by either means (hypertonic salt or deprivation) yielded quite similar curves.

Another possible objection was that these changes in the insulin action might be brought about by acidosis produced by the sodium chloride. This objection is categorically answered by the experiments illustrated by chart 4. Here the animal was flooded with fluids by the administration of 500 cc. of physiologic sodium chloride solution intra-

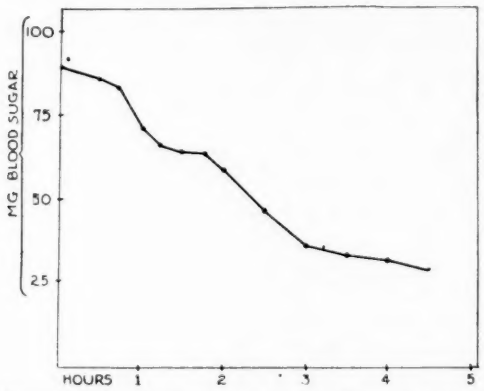

Chart 3.—Curve of dog dehydrated by forty-eight hours' deprivation (one-half unit of insulin per kilogram).

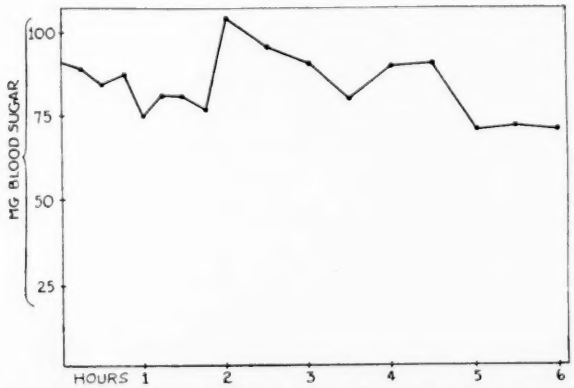

Chart 4.—Curve of dog hydrated by intra-abdominal injection of 500 cc. of physiologic sodium chloride solution the night before and 300 cc. more just before tests (one-half unit of insulin per kilogram).

peritoneally the afternoon before and 300 cc. more two hours before the experiment. He received 7.2 Gm. of salt as compared to 5.5 Gm. for the animal illustrated by curve 2. Therefore, if the acidosis was a factor one would expect the insulin effect to be even greater than in curve 2. Exactly the opposite takes place. In an animal overhydrated, flooded in

water as this one was, the insulin effect is almost abolished. There is a short fall in the blood sugar after which it rises to levels even higher than that at the beginning of the experiment (chart 4).

It is clear, therefore, that the degree of hydration of the tissues is the real factor in these variations. In dehydration the insulin effect is

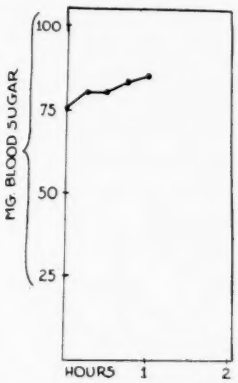

Chart 5.—Curve of dog after injection of epinephrine.

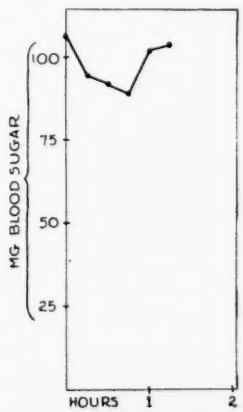

Chart 6.—Curve of dehydrated dog after injection of epinephrine.

intensified and prolonged and the opposite is true if there is a flooding of the body with fluids.

Interpretation of these phenomena is difficult. One cannot state categorically that more or less sugar is burned from such data as the above. Experiments with a gas exchange apparatus are being undertaken to settle this point. However, one would feel much inclined to doubt whether such relatively slight changes in the concentration of

insulin would be capable of producing such changes in its action. If we look a little deeper the question arises as to whether there is any variation in the mobilization of sugar in the body under these conditions. Normally, the injection of insulin not only brings about an oxidation of glucose in the tissues but it also causes a suprarenal stimulation which in turn causes an outpouring of sugar from the liver. As was noted above, in the dehydrated animals there was a lessening or absence of the preliminary rise in the blood sugar on insulin injection, and it therefore was thought possible that when the portal circulation was interfered with this epinephrine action on the liver (sugar mobilization) was interfered with, and that this might account for the length and depth of the insulin curve. In other words, the sugar burned was not replaced so promptly. The following experiments tend to confirm this view.

In apparently normal animals the injection of epinephrine brings about a slight rise in the sugar in the blood (chart 5). In animals who

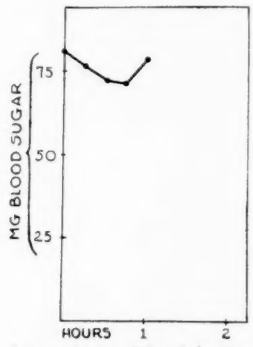

Chart 7.—Blood sugar changes caused by injection of epinephrine in patients with portal obstruction due to hepatic cirrhosis.

were dehydrated either by injection of hypertonic salt solution or by deprivation of water this epinephrine hyperglycemia does not occur. In fact, there is a gradual lowering of the blood sugar, due in all probability to the using up of larger amounts of fuel by the elevation of general tonus (chart 6). Chart 7 illustrates some experiments further confirming these facts. These are changes in the blood sugar brought about by the injection of epinephrine in patients with portal obstruction due to hepatic cirrhosis. It is evident then that interference with the portal circulation from general dehydration or from portal obstruction will prevent the mobilization of sugar from the liver by epinephrine.

COMMENT

From the foregoing experiments it is evident that our conceptions of sugar metabolism have overlooked an important source of error.

Numerous important applications at once suggest themselves. Among the most important I will briefly enumerate the following:

1. This factor must be considered in the standardization of insulin.

2. In postoperative acidosis, the value of fluids is given a rational basis. In the water starved tissues not enough sugar is mobilized from the liver to insure complete oxidation of fats.

3. The question of the amount of fluid in diabetic diets is given additional importance.

4. The protein sparing action of glucose in wasting disease especially cannot be exerted unless there is sufficient fluid in the body to provide an adequate mobilization of sugar from the liver. In most asthenic individuals, dehydration is marked.

CONCLUSIONS

1. Sugar metabolism, as illustrated by the fall in the blood sugar after administration of insulin, is profoundly influenced by the relative degrees of hydration of animals.

2. The intensity and duration of the fall in blood sugar after administration of insulin are enormously greater in animals who are dehydrated by various means, and much less in animals who are flooded with water.

CORRECTION

Dr. Arthur L. Bloomfield, Baltimore, calls attention to two errors occurring in the first formula in the paper by him and Doctor Keefer, "A Method for the Continuous Quantitative Estimation of Gastric Secretion and Discharge in Man," appearing in the June issue of the ARCHIVES OF INTERNAL MEDICINE (p. 822). The formula should read:

(1) $\left[\frac{x}{y} \times A\right] - A =$ maximum possible amount of juice secreted in ten minute period, in which

Book Reviews

PHYSIOTHERAPY. By HARRY EATON STEWART, M.D. New York: Paul B. Hoeber.

In the light of advances in the field in recent years, the writer adds to his previous works, "Diathermy and its Application to Pneumonia" and "Physical Reconstruction and Orthopedics", a volume on physiotherapy of fundamental simplicity and thoroughness.

Part 1 is a combination of instruction in physics, hospital management and physiology dealing with galvanism, ionization, sinusoidal and galvanic currents, faradism, static, high frequency, phototherapy, actinotherapy, thermotherapy, massage, exercise and hydrotherapy. Under each subject the principles involved are discussed in detail, the theoretical application and selection with reference to special conditions, both physiologic and mechanical, are dealt with and the comparative values discussed. With each there are careful plans and instructions for installation and use with photographs and plans of methods of application and equipment.

Part 2 is clinical with clinical application of the various methods to disease. Chapters are devoted to the neuromuscular systems, the bones and joints, the cardiovascular system, the gastro-intestinal tract, the respiratory system, the skin and the genito-urinary system.

Especially interesting are the results obtained in diphtheria cases with ultraviolet light, treatment of pyorrhea with quartz lamp and lobar pneumonia with diathermy. The results claimed in pneumonia are such that more information regarding diagnosis and controls is required and the results of similar series much be compared before they can be fully accepted. The author states that with one exception no patient has been lost who has been treated before the third day. The results in hypertension are not convincing of actual benefit.

In general, the author believes that the physician will be of greater value to his patient if his knowledge of physiotherapeutic methods permits him either to treat disease himself or to recognize the value in given cases and direct or advise their use. A careful study of the book is recommended to everyone.

A SYNOPSIS OF MEDICINE. Fourth Edition. By HENRY LETHEBY TIDY, M.A., M.D., B.Ch., Assistant Physician to St. Thomas' Hospital. Cloth. Price, $6. Pp. 1,000. New York: William Wood & Co., 1925.

In this synopsis the author strives to present the important principles of medicine in a manner that will enable the reader to grasp rapidly the essential features of any given condition. He has thus employed the outline form except in places in which more detailed information seemed necessary. The general arrangement of the book is similar to that of Osler's "Principles and Practice of Medicine." In the preparation of the volume, various standard textbooks, systems of medicine and monographs were consulted. In the present edition, considerable alterations have been made in the chapters on gallstones and bronchial asthma and in the subject of botulism. Visceroptosis, infarction of the lung, purpura and acholuric jaundice are carefully reconsidered. New chapters are added on the blood diseases of children and on thrombosis and embolism.

The book will satisfactorily serve the purpose for which it was written and thus be useful to the student, the practitioner or the teacher. It is, however, not intended to replace the standard textbook and should not be used in this capacity.

ARCHIVES OF THE ANDREW TODD MCCLINTOCK MEMORIAL FOUNDATION FOR THE STUDY OF DISEASES OF THE ALIMENTARY CANAL. VOLUME I. PLEOMORPHISM IN BACTERIAL PROTOPLASM—A STUDY IN PSITTACOSIS. By ANDREW TODD MCCLINTOCK, M.D. Edited by JOHN WILLIAM DRAPER. Privately printed, 1925.

The Andrew Todd McClintock Memorial was established by Isabel Cairns McClintock in memory of her husband, who died at the age of 38 of "chronic intestinal invalidism." Several of the productive years of Dr. McClintock's life were devoted to a study of the causes of disease of the gastro-intestinal tract and it was his intention to devote the remainder of his life to this study. When it was cut short by his untimely death, Mrs. McClintock established the memorial in order that further work in his favorite field might be continued in memory of him.

The first volume of the archives of this foundation consists in a manuscript that was found among Dr. McClintock's papers recording his own investigative work on psittacosis. The conclusions drawn by him are in part as follows: "An epidemic of disease among parrots occurred in Wilkes-Barre, Pa., March 2, 1917. This was followed by an epidemic among human beings. The cause of this epidemic was, originally, the chilling of the parrots, which, by changing the intestinal secretions, affected the generalized bacterial protoplasm in their intestines, so that it assumed powers of disease production in living tissues. Energy became extraordinarily heightened was concentrated, and associated matter, excessively light, was passed upon the surrounding air to human beings. It has been developed in this investigation that the type of the local epidemic was due to the general flexibility in the mechanism of character demonstration of the generalized bacterial protoplasm, saprophytic in the parrot intestines. The origin of the epidemic depended upon the arousal to an intense activity of that mechanism capable of creating an affinity for animal tissue."

The chief value of this monograph lies not in the work that it records on psittacosis or on pleomorphism in bacterial protoplasm, but in the intimate contact that it gives with the brilliant mind of a medical idealist. Here one sees a resourceful and powerful imagination that is balanced and checked by scientific trial and reason. The conclusions may be erroneous, but the ideas are delightfully stimulating.

THE ART OF MEDICAL TREATMENT. By FRANCIS W. PALFREY, M.D., Visiting Physician, Boston City Hospital; Instructor in Medicine, Harvard University. Cloth. Price, $4.50 net. Pp. 463. Philadelphia: W. B. Saunders Company, 1925.

The title of this work is alluring. The term "art" in relation to medical practice has been rather loosely used and various meanings have been ascribed to it; to some it may mean technical skill, to others the manner or "approach" of the physician in practice, while to others it may simply mean the ability to maintain the confidence of the patient by any means whatsoever. In the introduction Palfrey explains that the "practice of medicine is an art in which the teachings of medical science are put to their practical application"; includes not only the therapeutic and diagnostic measures used, but also the manner in which all dealings with the patient are conducted. . . . Attempt is here made to include, in addition to therapeutic measures in the narrower sense, something more of the art of medical treatment, by hinting what can be said, either in encouragement, in explanation or in warning to the patient and to his friends. . . . The art of medical treatment, therefore, includes both therapeutic measures in the narrower sense and information and mental guidance."

This idea is well carried out in the text. The work is similar in many respects to Shattuck's "Principles of Medical Treatment" and is condensed into a small volume. It is printed on good paper and the type is excellent; there

are no illustrations. The important infectious diseases and in addition those due to physical agents or poisons, diseases of nutrition and of metabolism and of the various systems of the body are considered. Each disease is discussed under such headings as first thoughts, placing, diet, remedial, supportive and palliative measures, minor care, nursing, information and preventive measures. Several appendixes are added on such subjects as stimulation, bed-sores, transfusion, diet and duodenal intubation. These add greatly to the interest and value of the book and are repeatedly referred to in the text.

The book should have a wide field of usefulness for both the student and the general practitioner because the information given is accurate and is clearly and briefly stated and the author displays good sound judgment throughout.